

HONG KONG PHARMACEUTICAL *JOURNAL*

VOL 30 NO 1 Jan - Apr 2023 ISSN 1727-2874



News & Short Communications

The Trend to Watch – Real-World Data & Real-World Evidence

Overview of the Drug Therapy of Psoriasis
(2 CE Units)

The Activities of the Society of Hospital Pharmacists

The Activities of the Pharmaceutical Society of
Hong Kong

Hong Kong Pharmaceutical Journal:
For Detailed Instructions for Authors



*The Pharmaceutical Society of Hong Kong
The Practising Pharmacists Association of Hong Kong
The Society of Hospital Pharmacists of Hong Kong*

The Trend to Watch – Real-World Data & Real-World Evidence

IU, Pui Chinga; CHONG, Donald Wing Kit^{a*}

^a GSK (Consumer Healthcare) HK Limited, 23/F, Tower 6, The Gateway, 9 Canton Road, Tsimshatsui, Kowloon, Hong Kong SAR, China (*Corresponding author)

ABSTRACT

With the advancement in data technology, the use of real-world data (RWD) is becoming a common approach in healthcare research. The potential of real-world evidence (RWE) in complementing randomized clinical trials (RCTs) has been acknowledged by regulatory authorities such as FDA and EMA. In near future, RWD/RWE will play a larger role in supporting regulatory decisions, such as drug approvals and expansion of indications. This article aims to provide pharmacists with an overview of RWD/RWE in terms of its strength and pitfalls. There will also be elaborations on the application possibilities of RWD/RWE in the whole drug product lifecycle, and the current status of real-world studies in Hong Kong. The integral role of pharmacists in understanding, communicating, and generating real-world data will also be discussed.

Keywords: Real-world Data, Real-world Evidence, Randomized Controlled Trials (RCTs), External Validity, Internal Validity

INTRODUCTION

Stakeholders in the healthcare ecosystem are always concerned about the cost and time it takes for new medical innovations to gain regulatory approval and market recognition. Over the decades, the magnitude of increase in drug development cost is in spiralling scale; with cost doubling every 9 years.^(1, 2) A median of 8 years (range 5-20 years) is required to move a new drug entity from lab bench to bedside, with 6-7 years spent on clinical trials.⁽³⁾ Regulatory agencies have been using randomized clinical trials (RCTs) as the benchmarking standard for market approval. However, RCTs are expensive, time-consuming, and are not fault-free experiment designs. Scholars and scientists are looking for newer research practices and ideas that could provide complementary evidence to RCTs.

DEFINITION OF REAL-WORLD DATA (RWD) AND REAL-WORLD EVIDENCE (RWE)

Studies derived from real-world data (RWD) are gaining the attention of healthcare stakeholders. They could aid in the safety and efficacy proof of medical interventions that were conventionally dominated by RCTs. “RWD” is not a new term; early traces of RWD are seen way back in literature from the 1980s.^(4, 5) However, there is no consensus on the definition of RWD, which prompted The U.S. Food and Drug Association (U.S. FDA) to put forward a definition, after recognizing its potential value in 2018.⁽⁶⁾ RWD is defined as “data related to patient health status or delivery of healthcare”, excluding those collected from RCTs. The evidence of potential benefits and risks of medical interventions derived from the evaluation of RWD is defined as real-world evidence (RWE).

FEATURES OF RWD

While RWD is often understood as a type of healthcare big data, they are not synonyms. The definition of RWD does not include a criterion for data size.⁽⁷⁾ However, the astonishing development speed of big data technology has potentiated RWD to function as a promising source of information to understand our health. Useful RWD generally processes the characteristic of big data, namely the 5Vs: “Volume”, “Variety”, “Velocity”, “Value” and “Veracity”.^(7, 8)

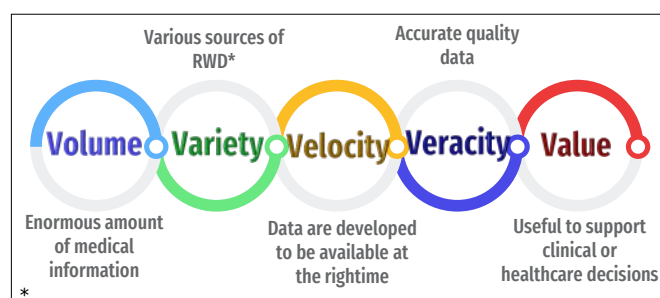


Figure 1: 5Vs of RWD/ RWE

The sources of RWD include, but are not limited to: electronic health records (eHRs); health financial claims and billings records; disease registries (databases storing patients' diagnoses); patient-generated data (such as blood glucose monitoring data in ambulatory settings); and data generated from medical devices (such as mobile wearable biosensors).⁽⁶⁾

THE TREND OF RWD AND HOW IS IT RELATED TO PHARMACY PRACTICE?

The application of RWD has been mainly on pharmacovigilance and post-marketing drug safety surveillance. In the last few years, regulatory agencies worldwide are opening their doors to use RWE for approval of pharmaceutical products and medical devices. The U.S. FDA was one of the first agencies to acknowledge RWD's importance. In 2016, the "21st Century Cures Act" was signed into law in the U.S., which aimed to accelerate the process of drug development.⁽⁶⁾ Under the provision of the Cures Act, U.S. FDA was called to develop a framework for RWD/RWE. The framework was issued two years later and provided guidance on the role and requirement of RWD/RWE in the approval of new drug indications and in supporting post-approval studies.⁽⁹⁾ The European Medicine Agency (EMA) also announced its vision for enabling RWD/RWE to be used in regulatory decision-making by 2025 in the 2020 strategic document, "Regulatory Science Strategy to 2025".⁽¹⁰⁾ In 2021, EMA issued the "Regulatory Science Research Needs Initiatives" which identified 15 RWD/RWE related topics in need of further research to address the current knowledge gap.⁽¹¹⁾

The worldwide effort to promote RWD/RWE is expected to impact the current process of drug approval, reimbursement, price negotiation, and also patient-care decision in near future.^(12, 13) In view of the transforming landscape of RWD, it is important for us, pharmacists, to have an overview of RWD, to: 1) understand more about its expanded applications in global and local domains, and 2) be able to evaluate the evidence derived from RWD for clinical and regulatory decisions.

CLARIFICATIONS ON SOURCES OF RWD & METHODOLOGIES OF RWE

Among the spectrum of potential RWD sources, one common misconception is that RWD only refers to retrospective data coming from routine healthcare databases. Routine healthcare data such as claims, electronic health records, and pharmacy retail records, are usually not developed with research intention. However, healthcare data could be collected actively, prospectively and under a pre-defined protocol to fulfil specific research purposes. These include well-designed disease registries and patient-generated data. While different types of RWD could come with specific advantages and disadvantages (illustrated in **Table 1**), their shared characteristic is that

they are health status-related data that are generated outside clinical trial setting.⁽¹⁴⁾

Another commonly confusing concept to be cleared up is the two related terms, RWD and RWE. RWE is the evidence generated from the analysis of RWD. When compared to RCT, the methodologies used to generate scientific and clinical evidence from RWD are far more complex and have greater variability. RWE studies are often described as observational studies, but they are not equivalent. Non-interventional observation study designs, often use RWD as their main source of data. These include cohort studies which could be prospective or retrospective in nature, retrospective case-control studies, and cross-sectional studies.⁽¹⁴⁾

On the other hand, interventional studies such as pragmatic trials (or pragmatic randomized control trials) (PCT) could also be used to generate RWE. The aim of RCTs can be described by a continuum between the two extremes: explanatory and pragmatic.^(15, 16) Traditional RCTs are more of an explanatory purpose which the main focus is to explore the effect of interventions; while PCTs aim to inform clinical and policy decisions.^(17, 18) Both RCT and PCT involve randomization for control to avoid potential bias. However, the level of randomization is lower in PCT which is only at cluster level (e.g. hospital level) but not individual level. The inclusion and exclusion criteria and the requirement for intervention adherence are also less stringent when compared to RCT. In this way, PCT could reflect effectiveness in usual care.

HOW RWE STUDIES COMPLEMENT RCTs

Large sample size

With the advancement of big data technology, RWD is able to provide a large heterogeneous sample in a much quicker and cheaper approach than RCT, and can provide opportunities in the study of rare diseases. Traditional RCTs on rare diseases are challenging in terms of patient recruitment and burden to test and measure outcomes.⁽²⁶⁾ Currently, only 5% of rare disease have approved treatment.⁽²⁷⁾ Hence, RWE studies may be one of the few feasible approaches to facilitate the evaluation of potential orphan treatments for rare diseases.

Efficacy and effectiveness

While RCTs are regarded as the gold standard for evaluating efficacy of interventions, RWE could provide supplementary evidence in effectiveness of the treatment.^(28, 29) In a general context, "efficacy" and "effectiveness" could be used mutually and reciprocally. However, in research, interventions are said to be "efficacious" if the desired effect could be demonstrated under well-defined and ideal circumstances. On the other hand, effective interventions are those which have capacity to produce expected performance in real-world practice. When compares to RCT, treatment patterns and

Table 1: Source of RWD			
Source of RWD ⁽¹⁹⁾	Examples	Advantages	Disadvantage
Claims ⁽²⁰⁾	• Medical insurance claims • Health Financial claims • Drug claims	• Applicable for countries/ regions implemented national medical insurance schemes • Cost-effective method of collection of readily available data • Patients with specific medical conditions are easily identified	• Validity of record may be limited as data are recorded for reimbursement purpose • Data shared between different agencies, some data details (e.g. adverse events, radiology and laboratory test results) may not be captured • Incomplete information regarding some sensitive diagnoses and medication dosages
Registries ⁽²¹⁾	• Disease registry (storage of patient diagnosis) • Product (drug and devices) registries (e.g. Pregnancy exposure registries) • Procedures or health service registries	• Well-designed registries could collect comprehensive information such as patient demographics, risk factors contributing to disease, disease progression, relapsing, remitting, and severity • Provide a large sample size of longitudinal data • Access long-term effectiveness and safety of interventions	• Prone to selection bias (most registries are voluntary, only those willing to participate are recruited) • Difficult to conduct data verification • Underestimation of events due to loss to follow-up, loose monitoring of patient's condition • Duplicate records due to anonymous data collection • Absent of control group
Clinical data ⁽²²⁾	• Electronic health records (eHRs) which include laboratory tests • Hospital billing data	• Reduce the cost and effort of data collection • Contains representable data from targeted group of patients • Provides comprehensive longitudinal data	• Statistical adjustment might be needed when conducting multiple hypothesis study, which may result in biased findings • eHR is not built for research purposes but is intended for clinical use, extensive data processing procedure may be required for data analysis • only capture patients' activities who utilize hospital services
Pharmacy/Retail record ^(23, 24)	• Drug sales data • Prescription data	• Allow the assessment of continuity of care for patients when integrated with eHR	• Non-unified standard of pharmacy data makes it difficult for data analysis
Patient generated data ⁽²⁵⁾	• Glucose monitoring data in ambulatory settings • Data generated from medical devices such as mobile wearable biosensors (heart rate, blood pressure etc) • Social media • Patient advocacy organization	• Suitable for the study related to non-prescription medications • Suitable for chronic disease studies	• Selection bias may arise as people with advanced age, lower education level, lower technology and health literacy may have lower usability

therapeutic outcomes involved in RWE studies are more complex. RWD provides data for evaluation of different treatment options which have not been compared head-to-head in RCT studies.⁽³⁰⁾ In addition, RWD studies could also aid with the assessment on epidemiology, treatment adherence and persistence, prescribing patterns and health resources cost-effectiveness.⁽³¹⁾

External validity and internal validity

RWE studies offer the strength of external validity. External validity, also known as generalizability, is the extent of applying the conclusion of the study on different patients, treatments, or other settings and circumstances. The setting of RCTs focuses on internal validity and is deemed to sacrifice its generalizability in real-world. Internal validity refers to the degree of confidence for the observed causal relationship is representing the truth in the group of population under study, but not due to systemic errors or random errors.⁽²⁹⁾ The imposition of inclusion and exclusion criteria in RCT study protocol is a standard practice. The advantages of this practice include

increasing the reliability and reproducibility of study outcomes in answering the research question; minimizing the probability of recruiting patients which may interfere with study results; and lessening risk of posing adverse events to vulnerable patients.⁽²⁶⁾ By adhering to the selection criteria in study protocols, RCTs could maximize the internal validity of the study.^(29, 32) However, individuals of extreme ages, multi-comorbidity, polypharmacy, and patients with difficulties complying with study protocols, are often underrepresented in RCTs.⁽²⁹⁾ Although good internal validity is the prerequisite of external validity,⁽³³⁾ RCTs with narrower population selection increase the difficulty of applying the results to routine clinical practice.

On the other hand, the sources of data from RWE usually contain a larger pool of heterogenous samples than RCTs. Treatment outcomes from RCT-excluded patients (such as elderly patients and renally repaired patients) could be retrieved and analysed in RWE studies.^(31, 34) RWE can supplement RCT by providing a greater external validity from their findings.

An example showing the gap between RCTs sample population and real clinical practice population was illustrated by Kennedy-Martin et.al⁽³⁵⁾ in a literature review on RCTs to examine their external validity. The review included 52 RCTs on oncology, mental health and cardiology. The review evaluated the RCTs by two methods: (1) comparing the demographics of sample population in RCTs statistically with patients in routine clinical practice, or (2) determined the ineligibility rates of real-world patients that could not satisfy the inclusion criteria of the RCTs. It was found that real-world patients often had higher risk characteristic when compared to RCTs samples. These risk factors included older age, worse disease prognosis, more co-morbidities and less likely to receive guideline-recommended therapies. In all three studied disease areas, the majority of the RCTs reviewed had a real-world ineligibility rate greater than 50% (44.4% for cardiology, 88.9% for mental health, and 66.7% for oncology). The author suggested that more restrictive criteria used in sample selection (for higher internal validity) signifies greater difficulty for the RCT to provide an accurate perspective of drug efficacy and safety in real-world clinical practice.

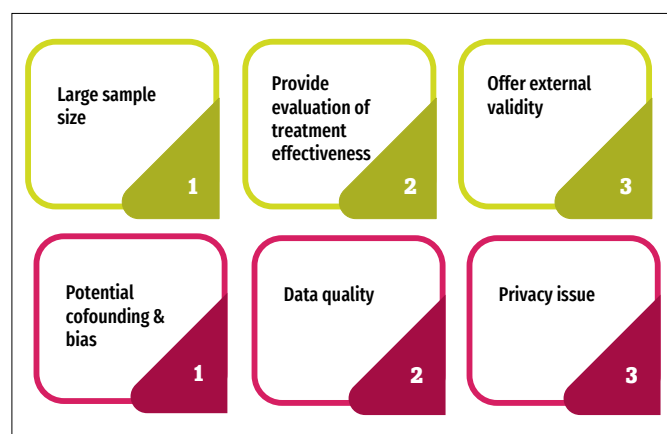


Figure 2: Strength and Pitfalls of RWD/RWE

POTENTIAL IMPEDIMENTS OF RWE

While RWE gives higher generalizability than RCT, there are intrinsic limitations constraining its acceptance from some researchers. In the evidence hierarchy of evidence-based medicine, RCT is ranked as the most scientific vigorous research method among single study settings. The robustness of RCTs attributes to the randomization process which reduces between-group-comparability. The baseline demographics between the treatment group and control group are balanced, which lowers selection bias and minimizes confounding factors when identifying cause-to-outcome relationships⁽²⁸⁾ For RWE studies, many pitfalls need to be carefully watched over when expanding its use. Despite that, many of these limitations are well-recognized by researchers. Different measures have been taken to optimise the potential uses of RWD sources and RWE studies.

Cofounding & bias

The lack of randomization increases the risk of cofounding and bias in RWE studies. Cofounding refers to some unobservable or unmeasured variables which could affect the cause-effect analysis of a study.⁽³¹⁾ Major bias in RWE studies includes selection and information bias. Selection bias arise when there are factors during the patient selection process that could influence the representativeness of the intended population to be studied. For example, data from healthier and younger patients tend to be more available from insurance claims.⁽³⁶⁾ Information bias includes recall bias, and reporting bias which may be prominent in patient-generated data.

To minimize bias and adjust for cofounding factors, strategies depending on the type of cofounders (measured cofounders, unmeasured but measurable cofounders, and unmeasurable cofounders) can be utilized.⁽³⁷⁾ For measured cofounders, statistical methodologies such as restriction and stratification of types of patients, matching of controls, and propensity scores are used.⁽³⁸⁾ In particular, propensity score is a popular statistical tool in observation studies which could be used to adjust for the treatment effect. This is done by calculating the probability of patients receiving the treatment option based on different measured factors (e.g. age and sex).⁽³⁹⁾ For accounting unmeasured but detectable cofounders, approaches such adjustment using external data and proxy measurement could be employed. For example, Danish National patient registry, diagnosis of chronic obstructive lung disease (COPD) is used as a proxy marker of previous smoking history.⁽³⁷⁾ To address unmeasurable cofounding factors, some studies may be able to use self-controlled designs, and sensitivity analysis to ensure the robustness of the assessment. Instrumental variables are also a potential way to control cofounding. Instrument variables are variables which covary with the predictor variables but have no effects on the dependent variables. A real-world study aiming to access the effectiveness of nonsteroidal anti-inflammatory drug (NSAIDs) on the treatment of patent ductus arteriosus (PDA) in preterm Infants utilized instrumental variables. The instrument used was institutional variation in NSAIDs prescribing frequency. This instrument variable is incorporated into the analysis to illustrate the effect of the predictor variable (NSAIDs exposure) on the dependent variable (PDA closure).⁽⁴⁰⁾

Missing data and lack of data consistency

Many RWDs, such as eHRs, are considered as refined and structured databases and have great potential to support RWE studies. However, eHRs are primarily built for routine clinical practice and are not intended for research studies. When data are extracted from eHRs for research, their unique complexity and significant inaccuracies become visualized to the researchers. For example, manual entering of eHR often embedded with various transcription errors which are difficult to trace. In addition, non-numerical characters, free texts, unstandardized abbreviations are commonly found in

eHRs.⁽⁴¹⁾ Thus, direct data analysis is often impossible, as researchers need to go back to review the original patient chart and make data modifications. Some patient demographics such as height and weight may not be routinely measured or may rely on patient reported value. Furthermore, the change of these demographics over the treatment period may not be recorded, which may become an unaccounted covariate or cofounder in the study.⁽⁴¹⁾

Different initiatives have been proposed to leverage data standardisation from RWD. To facilitate the electronic exchange of clinical information, electronic documentation and entry should use consistent terminologies. For example, Systematized Nomenclature of Medicine, Clinical Terms (SNOMED-CT) and International Classification of Diseases (ICD) are universal languages of healthcare that could be adopted.⁽⁴²⁾ Computer translation programs is a solution to tackle unstandardized images, signals or any other form of clinical data.⁽⁴³⁾ An international collaborative, the Observational Health Data Sciences and Informatics (OHDSI), was initiated to explore different data models to transform medical data into a consistent manner for research purpose, and allows researchers to utilize its open network as a data holder, as every element in the original data will be mapped to common vocabularies within the data model. This international effort is important in facilitating world-wide multicentred studies and expanding the feasibility of RWE studies.⁽⁴⁴⁾

REGULATORY & PRIVACY ISSUES

There are three aspects in the main footing of regulatory bodies on RWE regulation: (1) the establishment of regulatory frameworks to outline the use of RWE in the product lifecycle; (2) creating consensus and guidance for standardization of RWE study designs and data management; (3) addressing data privacy issues relating to RWD.^(45, 46)

Regulatory frameworks for RWE

A clear regulatory framework for RWE is vital to expand the usage of RWE usage in product life-cycle. The FDA RWE framework was first released in 2018 as mandated under 21st Century Cures Act. In October 2022, an official guidance on submitting documents using RWD to FDA for drug and biological products was issued. The final guidance included a list of proposed purposes for RWD/ RWE for the support of changes in indication; changes in dose, regimen and route of administration; adding new patient population; adding comparative effectiveness information and safety information, etc.⁽⁴⁷⁾ Other regulatory agencies, such as European Medicines Agency (EMA) and the European Commission, Medicine and Healthcare Products Regulatory Agency of United Kingdom, National Medical Products Administration (NMPA) in China, the Taiwan Food and Drugs Administration (TFDA) have either released similar guidance documents or are in

the process of generating one. Other countries such as Singapore, South Korea, Australia and New Zealand have been showing increasing interest in broadening the use of RWE in regulatory decision making.⁽⁴⁵⁾

Guidelines for standardization of RWE study designs and data management

The quality of RWD database and RWE study design are also concerns of regulatory agencies. When evaluating evidence derived from RWD, there should be no “one size fits all” approach.⁽⁴⁸⁾ However, general requirements still hold, such as whether the RWD is fit for the study purpose, and the adequacy of scientific evidence provided by the RWE study design.⁽⁴⁵⁾ The FDA introduced the Advanced RWE program in October 2022, which allows for sponsors to discuss the RWE study protocol with agency staff before initiation. This program aims to ensure RWE study designs and the proposed data processing approach meets the approval requirement, subsequently promoting coherent regulatory decision making.⁽⁴⁹⁾

Privacy & Security Issues

The limit of access to data is one of the challenges for pharmaceutical companies or researchers when conducting RWE studies.⁽⁴⁶⁾ There is always a contradiction between data security and privacy, and the use of RWD. RWD could process a massive amount of personal sensitive data, such as health status, medical histories, financial status, social patterns and correlations.⁽³⁸⁾ During RWE studies, information from different databases (e.g. eHR, claims etc) may be retrieved and linked for analysis. This poses privacy risks for any unauthorized use or unlawful surveillance of data to reveal personal pattern and correlations.

Currently, many countries worldwide have imposed regulations regarding data protection. For example in UK and EU, the collection, storage, sharing and analysis of healthcare data are governed under the international privacy law, General Data Protection Regulation (GDPR).⁽⁵⁰⁾ To balance the need for data protection and facilitate RWE research, appropriate legal basis should be established. Defined guidelines should be available for researchers and pharmaceutical companies to ensure data privacy principles (lawfulness, fairness and transparency, purpose limitation, data minimization, storage limitation, integrity and confidentiality, and accountability) could be achieved throughout the big data security lifecycle (data collection, data transformation, data modelling, and knowledge creation phases).⁽³⁸⁾ The regulations need to be up-to-date and compatible with the evolving big data technology and its data security technology. Some examples of state-of-art approaches and technologies to control data privacy includes authentication by transport layer security (TLS) or secure sockets layer (SSL); data encryption algorithms; data-masking by k-anonymization and differential privacy; access controls based on roles and attributes; monitoring and auditing of network traffics to prevent intrusion.⁽⁵¹⁾

THE APPLICATION OF RWD / RWE IN WHOLE PRODUCT LIFECYCLE

RWD has long been used for pharmacovigilance activities and post-marketing effectiveness assessment. Other potential usages of RWD / RWE have been assessed in pre-market authorization stages of the product lifecycle by regulators. RWD is a great data source for studying disease epidemiology, treatment patterns and outcomes, and burden of disease.^(52, 53) RWD helps streamline the drug development process, provides evidence for effectiveness for new medical innovations, drives the repurposing of post-market drugs, and may transform healthcare decision making.⁽⁵²⁾ In addition to supporting pharmacovigilance activities, other usages of RWE throughout the product lifecycle are discussed below.

Early drug development: Application on disease strategy and providing insight for research

The influence of RWD could happen early in drug discovery stages, through identifying unmet needs and burden in disease management. Researchers could assess RWD for studying disease epidemiology information such as incidence and prevalence of a disease, risk factors for disease, and to project opportunities of preclinical developments.^(54, 55) RWE plays an important role in research concerning chronic diseases, as RCTs are often time limited.⁽⁵⁶⁾ Kong et.al⁽⁵⁷⁾ conducted a cross-sectional study based on the data retrieved from Joint Asia Diabetes Evaluation (JADE) register database, to explore the patterns of insulin usage and glycaemic control in Asian people. Through the RWD source, the study was able to identify the association of multiple factors on HbA1c target attainment and hypoglycaemic events, such as type of insulins, diabetic kidney disease status and young-onset diabetes. The study revealed an

unmet medical need of a generally poor glycaemic control in Asian population, and called for further support on diabetes research, patient education and engagement.

Application on Clinical study

While designing a traditional RCT, restrictive criteria is imposed in the trial protocol to ensure internal validity of the study. Very often, these criteria lack support and may hamper the generalizability of the study. There were numerous cases of post-marketing withdrawal due to safety issues when the drugs are applied to a broader patient population. These incidences alerted regulators regarding the limitation of RCTs.⁽⁵³⁾ RWE can assist the modification of RCT design by optimizing patient recruitment criteria. The selection criteria could be based on the evaluation of information such as target patient demographics, disease risk factors, treatment options from RWD. Besides, RWE could also aid in the estimation of required sample size,⁽⁵⁸⁾ and aid in the selection of suitable surrogate markers.⁽⁵⁵⁾

RWD can also provide historical controls for clinical trials, and has long been used as a source for historical controls. There are situations where RCTs are not feasible, such as ethical barriers to use inferior treatment options in the control group, or recruitment difficulties in the studies of rare diseases.⁽⁵⁹⁾ One early example of using historic controls for approvals by a regulatory agency was Lepirudin in 1998. Lepirudin is used in the treatment of immunologic type of Heparin-associated thrombocytopenia. The source of RWD used was registry data on subjects who was not treated with the recombinant hirudin. When comparing the treatment and historical control group, the study demonstrated a lower incident rate in the treatment group.⁽⁶⁰⁾ Although Lepirudin was later discontinued due to commercial decision, the

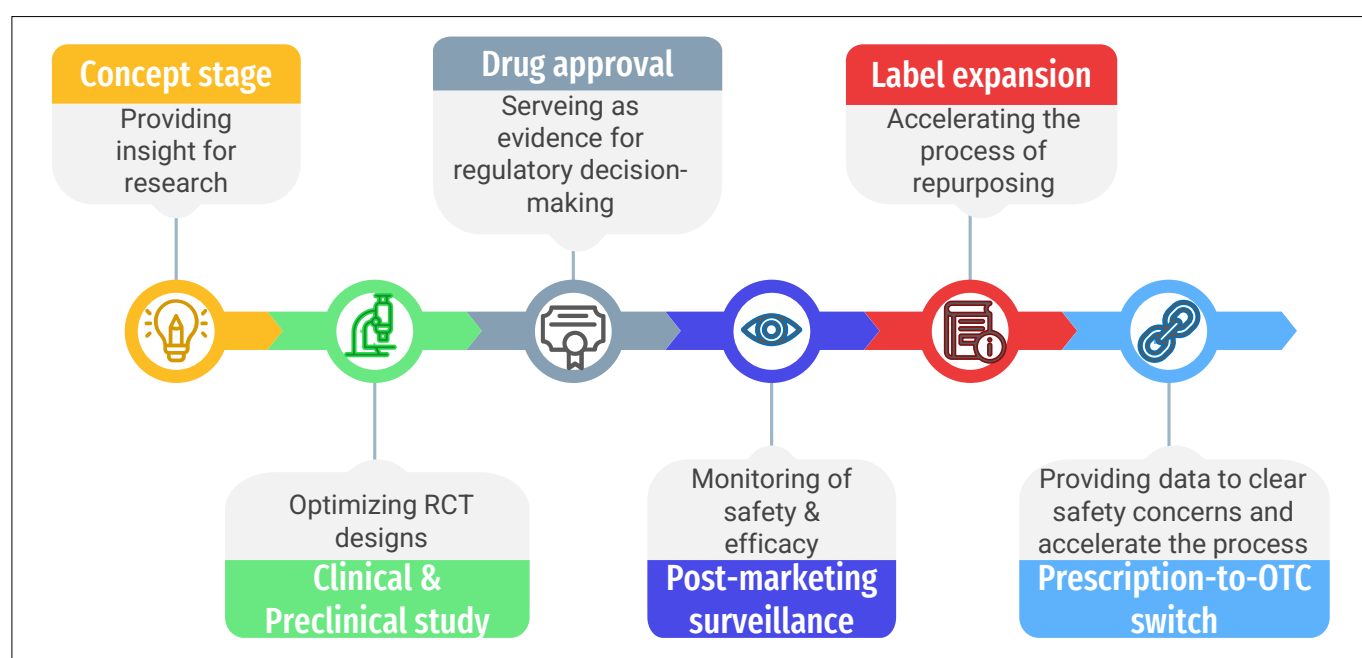


Figure 3: Application of RWD/ RWE in pharmaceutical products lifecycle

case opened the door to RWE as a support for regulatory drug approval. Over the years, the use of RWD for new drug application has extended to different therapeutic areas, with the most common areas being oncology, rare metabolic diseases and immunology.⁽⁶¹⁾

Supporting post-marketing activities

Aiding post-marketing safety and efficacy studies

The benefit-risk profile surveillance of post-marketing medical products is an acknowledged application of RWD and RWE. According to a systemic review on the types of evidence used in post-marketing authorisation referrals in European Union from 2013-2017,⁽⁶²⁾ RWE used in non-interventional studies provided evidence for 59% and 34% of 52 referrals for the evaluation of drug safety and drug efficacy respectively. Instead of primarily using it as leading evidence for regulatory decision-making, most of the RWE used in the referrals are cited as substantial evidence when comprehensive assessment was conducted.

One recent example of using RWE in addressing post-marketing safety concern was on the association between ibuprofen and severe coronavirus disease 2019 (COVID-19) infection.⁽⁶³⁾ Following the first detection of COVID-19 in late 2019, there was a hypothesis that the use of nonsteroidal anti-inflammatory drugs (NSAIDs) could promote the symptoms of COVID-19. A nationwide research conducted in Denmark based on the data from Danish National Patient Registry resolved the concern. The study compared the outcomes of COVID-19 between NSAID users and non-NSAID users, in terms of mortality, hospitalisation and intensive care admission. The study confirmed that there is no significant difference between the two groups of patients across different COVID-19 outcomes.⁽⁶⁴⁾

Expanding labelling & indications

The procedures for repurposing existing drug entities for new approvals are not straightforward. Many of the approved new indications still involved RCTs. A proper clinical trial is conventionally recommended to support labelling change to minimize patient risk from off-label usage of drugs. However, RCTs are known to be costly and time-consuming. In U.S., E.U and some other countries, temporary market exclusivity or similar incentive programs are used to encourage manufacturers for conducting trials for drug repurposing. However, these incentive programs may become valueless for market authorization holders if the off-label use of its generic competitors is common in routine prescription.⁽⁶⁵⁾

The adoption of RWE for new indication approvals is a policy advancement of FDA and may accelerate the process.⁽⁶⁶⁾ Between 2012 and 2019, 10 products (including one device) submitted their new indication application with the support of RWE to EMA and FDA. Japan is one of the frontier Asian countries in exploring

RWE.⁽⁶¹⁾ In 2016, it approved the use of the second-generation selective oestrogen receptor modulators, Raloxifene, in osteoporosis, based on RWE study using retrospective analysis of hospital claims database.^(53, 67)

Prescription-to-OTC switch

Prescription-to-over-the counter (Rx-to-OTC) switches is a conceivable opportunity for RWE. Rx-to-OTC switch is the change in marketing status from prescription drug product to non-prescription item. It is recognized by FDA as an important step to improve patient access to effective drug, empower patients on their own healthcare, and lower the healthcare burden due to unnecessary medical care.^(63, 68) Rx-to-OTC switch is a data-driven process, which needs to be supported by established scientific evidence on drug safety and efficacy. According to a report from IQVIA, a leading data and analytics solution provider in life science industry, RWE could provide information to access patient's ability to self-diagnosis, self-medication and economic benefits related to switching. These are all critical concerns to address before any switches decisions.⁽⁶⁹⁾

REAL WORLD STUDY IN HONG KONG

In Hong Kong, the number of published studies utilizing RWD increased significantly after the implementation of eHR system in 2016. In 2022, a retrospective cohort study was conducted on the effectiveness of the two antivirals available for COVID-19 patients in Hong Kong, molnupiravir and nirmatrelvir-ritonavir.⁽⁷⁰⁾ Using eHR from the Health Authority as a major RWD source, the timeline of the study from commencement to publication was significantly shortened into 8 months; and a significant number of samples was collected from 40,000 hospital in-patients. The study provided timely clinical evidence to support the use of antivirals in the ongoing pandemic of COVID-19.

The use of eHR data in Hong Kong is protected under Cap. 625 Electronic Health Record Sharing System Ordinance and Cap 486 Personal Data (Privacy) Ordinance.^(71, 72) Most local real-world studies based on eHR are at institutional level or in public hospitals. Currently, the Hospital Authority is opening access of clinical data to universities for use in research through the Clinical Data Analysis and Reporting System (CDARS). However, the access such data by private pharmaceutical companies are still planning afoot. Hong Kong has outlined the ambition to become a world-leading biotechnology data hub, but there is a need to strengthen Hong Kong's health data infrastructure, and promote academic-industry collaboration and technology transfer.⁽⁷³⁾ However, as Hong Kong has strong research credentials, many multinational pharmaceutical companies choose Hong Kong as one of the major sites to conduct clinical trials in Asia.⁽⁷³⁾ As RWD has been exercising its potential in aiding clinical trials worldwide, Hong Kong must catch up with the trend and come up with a balanced solution to

allow greater availability of health data whilst minimising risks to privacy and security.

ROLE OF PHARMACIST IN THE ERA OF REAL-WORLD DATA

Evidence-based pharmaceutical care is an imperative concept that shifted the modern role of pharmacists. In addition to evidence from RCT, it is increasingly important to consult practice-based evidence to support clinical decision making. RWD is a powerful data source to support the generation of these evidence.⁽⁷⁴⁾

Entering the era of real-world data, pharmacists may find growing responsibility in interpreting and evaluating RWE in the decision-making process. Shirley Wang, the principal investigator of the FDA Sentinel Innovation Centre, provided advices for new reviewers on assessing and interpreting RWE studies.⁽⁷⁵⁾ To ensure a piece of RWE is applicable, reviewing the relevancy of research question, the validity of the study design and the quality of data is a systematic approach. Identifying the research question is the priority. The PICOT framework is a helpful tool to access whether the RWE is relevant to the clinical inquiry or needs to be addressed, in terms of Population (P), Intervention (I), comparator (C), outcome (O) and Timing (T). While RWE studies are usually complex in study design, reviewer should be acquainted with the basic knowledge of strength and weakness of each type of RWE in different setting. One problem of RWE is that they usually report vague temporality. One simple way is to look for a study design diagram in the paper or construct one by oneself for interpretation of appropriateness of study entry point, and follow-up timing.⁽⁷⁶⁾ The relevancy of the data determines the credibility of the research. Data Reliance is the question of whether the data is complete and accurate. While most pharmacists are not well-trained in data science, as a reviewer, we could look for any description in data collection, cleaning, quality control and transformation in the paper and any attempts to address potential information bias.⁽⁷⁵⁾

Besides acting as a reviewer for RWE, pharmacists and other healthcare professionals should be more alert of their subtle participation in the RWE studies. To make eHR and other source of RWD develop into a fit-for-purpose research dataset and facilitate the generation of high-quality clinical evidence, this may also require pharmacists to provide domain expertise from time to time. When conducting RWE studies, communication between data scientist and healthcare professionals is valuable to balance the need of technical feasibility and addressment to clinical realities. Furthermore, as research data are generated from routine clinical practice in RWE studies,⁽⁷⁴⁾ quality assurance and control processes should start from data entry. As data could be expanded from one single patient to a potential cohort of patients who might benefit from RWE studies, pharmacists must remain vigilant in securing informatics competencies.

Author's background

IU Pui Ching was a pharmacy intern at GSK (Consumer Healthcare) HK Limited. For more information about this article, please contact her through her email address: iris.iupc@gmail.com.

CHONG Donald Wing Kit is current the Regulatory Affairs Director of GSK (Consumer Healthcare) HK Limited. His email address is: donald.x.chong@haleon.com.

References

1. Wouters, O.J., M. McKee, and J. Luyten, Estimated Research and Development Investment Needed to Bring a New Medicine to Market, 2009-2018. *JAMA*, 2020. 323(9): p. 844-853.
2. Yildirim, O., et al., Opportunities and Challenges for Drug Development: Public-Private Partnerships, Adaptive Designs and Big Data. *Frontiers in Pharmacology*, 2016. 7.
3. Dean G. Brown , H.J.W., Abhijeet Kapoor , Leslie A. Kenna, Noel Southall. Clinical development times for innovative drugs. 2021; Available from: <https://www.nature.com/articles/d41573-021-00190-9>.
4. Ronis, D.L. and K.A. Harrison, Statistical interactions in studies of physician utilization. Promise and pitfalls. *Med Care*, 1988. 26(4): p. 361-72.
5. Briscoe, J., Intervention studies and the definition of dominant transmission routes. *Am J Epidemiol*, 1984. 120(3): p. 449-55.
6. Administration, U.S.F.D., Framework for FDA's Real-world-evidence program. December, 2018.
7. Okada, M., Big data and real-world data-based medicine in the management of hypertension. *Hypertension Research*, 2021. 44(2): p. 147-153.
8. Lu, Z.K., et al., Big Data and Real-World Data based Cost-Effectiveness Studies and Decision-making Models: A Systematic Review and Analysis. *Front Pharmacol*, 2021. 12: p. 700012.
9. Real-world data (RWD) and real-world evidence (RWE) are playing an increasing role in health care decisions, FDA, Editor. 2022: U.S.
10. EMA Regulatory Science to 2025, E.M. Agency, Editor. 2020.
11. Regulatory Science Research needs. 2021, European Medicines Agency (EMA).
12. Pulini, A.A., et al., Impact of Real-World Data on Market Authorization, Reimbursement Decision & Price Negotiation. *Ther Innov Regul Sci*, 2021. 55(1): p. 228-238.
13. Rahmatian, D. and M. Tadrus, Old dog with new tricks: An introduction to real-world evidence for pharmacists. *American Journal of Health-System Pharmacy*, 2021. 78(24): p. 2277-2280.
14. Liu, M., et al., Toward a better understanding about real-world evidence. *European Journal of Hospital Pharmacy*, 2022. 29(1): p. 8-11.
15. Dal-Ré, R., P. Janiaud, and J.P.A. Ioannidis, Real-world evidence: How pragmatic are randomized controlled trials labeled as pragmatic? *BMC Med*, 2018. 16(1): p. 49.
16. MacRae, K.D., Pragmatic Versus Explanatory Trials. *International Journal of Technology Assessment in Health Care*, 1989. 5(3): p. 333-339.
17. Kevin Weinfurt, K.S., Jonathan McCall, Liz Wing. Differentiating Between RCTs, PCTs, and Quality Improvement Activities. 2017; Available from: <https://rethinkingclinicaltrials.org/chapters/pragmatic-clinical-trial/what-is-a-pragmatic-clinical-trial-3/>.
18. Zuidgeest, M.G.P., et al., Series: Pragmatic trials and real world evidence: Paper 5. Usual care and real life comparators. *J Clin Epidemiol*, 2017. 90: p. 92-98.
19. Chodankar, D., Introduction to real-world evidence studies. *Perspect Clin Res*, 2021. 12(3): p. 171-174.
20. Ahn, E.K., A brief introduction to research based on real-world evidence: Considering the Korean National Health Insurance Service database. *Integr Med Res*, 2022. 11(2): p. 100797.
21. Galluccio, F., et al., Registries in systemic sclerosis: a worldwide experience. *Rheumatology (Oxford)*, 2011. 50(1): p. 60-8.
22. Sauer, C.M., et al., Leveraging electronic health records for data science: common pitfalls and how to avoid them. *Lancet Digit Health*, 2022.
23. National Academies of Sciences, E., et al., The National Academies Collection: Reports funded by National Institutes of Health, in Real-World Evidence Generation and Evaluation of Therapeutics: Proceedings of a Workshop. 2017, National Academies Press (US) Copyright 2017 by the National Academy of Sciences. All rights reserved.: Washington (DC).
24. Maeda, H. and D.B. Ng, Regulatory Approval With Real-World Data From Regulatory Science Perspective in Japan. *Front Med (Lausanne)*, 2022. 9: p. 864960.

25. Jung, S.Y., et al., Development of Comprehensive Personal Health Records Integrating Patient-Generated Health Data Directly From Samsung S-Health and Apple Health Apps: Retrospective Cross-Sectional Observational Study. *JMIR Mhealth Uhealth*, 2019. 7(5): p. e12691.
26. Moore, J., et al., What role can decentralized trial designs play to improve rare disease studies? *Orphanet Journal of Rare Diseases*, 2022. 17(1): p. 240.
27. WILLMER, G., The building blocks to make rare disease treatments more common. 2022, Horizon, The EU research & Innovation Magazine.
28. Kim, H.S., S. Lee, and J.H. Kim, Real-world Evidence versus Randomized Controlled Trial: Clinical Research Based on Electronic Medical Records. *J Korean Med Sci*, 2018. 33(34): p. e213.
29. Monti, S., et al., Randomized controlled trials and real-world data: differences and similarities to untangle literature data. *Rheumatology*, 2018. 57(Supplement_7): p. vii54-vii58.
30. Araujo, S. How Real-World Data Supports Pharmaceutical Drug Development. 2022; Available from: <https://www.spiceworks.com/tech/big-data/guest-article/data-supports-pharmaceutical-drug-development/>.
31. Camm, A.J. and K.A.A. Fox, Strengths and weaknesses of 'real-world' studies involving non-vitamin K antagonist oral anticoagulants. *Open Heart*, 2018. 5(1): p. e000788.
32. Mickenautsch, S., Systematic reviews, systematic error and the acquisition of clinical knowledge. *BMC Medical Research Methodology*, 2010. 10(1): p. 53.
33. Hogarth, R.M., The challenge of representative design in psychology and economics. *Journal of Economic Methodology*, 2005. 12(2): p. 253-263.
34. Maissenhaelter, B.E., A.L. Woolmore, and P.M. Schlag, Real-world evidence research based on big data. *Der Onkologe*, 2018. 24(2): p. 91-98.
35. Kennedy-Martin, T., et al., A literature review on the representativeness of randomized controlled trial samples and implications for the external validity of trial results. *Trials*, 2015. 16(1): p. 495.
36. Togo, K. and N. Yonemoto, Real world data and data science in medical research: present and future. *Japanese Journal of Statistics and Data Science*, 2022. 5(2): p. 769-781.
37. Nørgaard, M., V. Ehrenstein, and J.P. Vandenbroucke, Confounding in observational studies based on large health care databases: problems and potential solutions - a primer for the clinician. *Clin Epidemiol*, 2017. 9: p. 185-193.
38. Liu, F. and P. Demosthenes, Real-world data: a brief review of the methods, applications, challenges and opportunities. *BMC Medical Research Methodology*, 2022. 22(1): p. 287.
39. Nguyen, T.-L., et al., Double-adjustment in propensity score matching analysis: choosing a threshold for considering residual imbalance. *BMC Medical Research Methodology*, 2017. 17(1): p. 78.
40. Slaughter, J.L., et al., Comparative Effectiveness of Nonsteroidal Anti-inflammatory Drug Treatment vs No Treatment for Patent Ductus Arteriosus in Preterm Infants. *JAMA Pediatr*, 2017. 171(3): p. e164354.
41. Kim, H.S. and J.H. Kim, Proceed with Caution When Using Real World Data and Real World Evidence. *J Korean Med Sci*, 2019. 34(4): p. e28.
42. Hovenga, E., Chapter 1 - Transforming health care, in Roadmap to Successful Digital Health Ecosystems, E. Hovenga and H. Grain, Editors. 2022, Academic Press. p. 1-16.
43. Cios, K.J. and G.W. Moore, Uniqueness of medical data mining. *Artif Intell Med*, 2002. 26(1-2): p. 1-24.
44. Hripcsak, G., et al., Observational Health Data Sciences and Informatics (OHDSI): Opportunities for Observational Researchers. *Stud Health Technol Inform*, 2015. 216: p. 574-8.
45. Burns, L., et al., Real-World Evidence for Regulatory Decision-Making: Guidance From Around the World. *Clinical Therapeutics*, 2022. 44(3): p. 420-437.
46. Hiramatsu, K., et al., Current Status, Challenges, and Future Perspectives of Real-World Data and Real-World Evidence in Japan. *Drugs - Real World Outcomes*, 2021. 8(4): p. 459-480.
47. USFDA, Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drug and Biological Products Guidance for Industry. 2022, U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), Oncology Center of Excellence (OCE).
48. Concato, J. FDA Draft Guidance on Real-World Evidence. 2022; Available from: <https://cdicollab.cdri.duke.edu/sites/NIHKKR/KR/GR-Slides-06-24-22.pdf>.
49. USFDA, Advancing Real-World Evidence Program. 2022.
50. Mulryne, J. Regulatory and Data Privacy Issues relating to Real World Evidence. The Journal of mHealth 2021; Available from: <https://thejournalofmhealth.com/regulatory-and-data-privacy-issues-relating-to-real-world-evidence/>.
51. Abouelmehdi, K., A. Beni-Hessane, and H. Khaloufi, Big healthcare data: preserving security and privacy. *Journal of Big Data*, 2018. 5(1): p. 1.
52. Berger, M.L., et al., Good practices for real-world data studies of treatment and/or comparative effectiveness: Recommendations from the joint ISPOR-ISPE Special Task Force on real-world evidence in health care decision making. *Pharmacoepidemiol Drug Saf*, 2017. 26(9): p. 1033-1039.
53. Khosla, S., et al., Real world evidence (RWE) - a disruptive innovation or the quiet evolution of medical evidence generation? *F1000Res*, 2018. 7: p. 111.
54. Yanfang Liu, H.Q., Paul Stang, Jesse A. Berlin. Real World Data: A Rich Resource for All Stages of Drug Development and Marketing. 2018.
55. Naidoo, P., et al., Real-world evidence and product development: Opportunities, challenges and risk mitigation. *Wiener klinische Wochenschrift*, 2021. 133(15): p. 840-846.
56. National Academies of Sciences, E., et al., The National Academies Collection: Reports funded by National Institutes of Health, in Examining the Impact of Real-World Evidence on Medical Product Development: Proceedings of a Workshop Series, C. Shore, et al., Editors. 2019, National Academies Press (US) Copyright 2019 by the National Academy of Sciences. All rights reserved.: Washington (DC).
57. Kong, A.P.S., et al., Real-world data reveal unmet clinical needs in insulin treatment in Asian people with type 2 diabetes: the Joint Asia Diabetes Evaluation (JADE) Register. *Diabetes Obes Metab*, 2020. 22(4): p. 669-679.
58. Martina, R., et al., The inclusion of real world evidence in clinical development planning. *Trials*, 2018. 19(1): p. 468.
59. Ghadessi, M., et al., A roadmap to using historical controls in clinical trials - by Drug Information Association Adaptive Design Scientific Working Group (DIA-ADSWG). *Orphanet Journal of Rare Diseases*, 2020. 15(1): p. 69.
60. Greinacher, A., et al., Heparin-induced thrombocytopenia with thromboembolic complications: meta-analysis of 2 prospective trials to assess the value of parenteral treatment with lepirudin and its therapeutic aPTT range. *Blood*, 2000. 96(3): p. 846-51.
61. Bolisli, W.R., M. Fay, and T.C. Kühler, Use of Real-world Data for New Drug Applications and Line Extensions. *Clinical Therapeutics*, 2020. 42(5): p. 926-938.
62. Brown, J.P., et al., Use of real-world evidence in postmarketing medicines regulation in the European Union: a systematic assessment of European Medicines Agency referrals 2013-2017. *BMJ Open*, 2019. 9(10): p. e028133.
63. Csoke, E., et al., How can real-world evidence aid decision making during the life cycle of nonprescription medicines? *Clin Transl Sci*, 2022. 15(1): p. 43-54.
64. Kragholm, K., et al., Association Between Prescribed Ibuprofen and Severe COVID-19 Infection: A Nationwide Register-Based Cohort Study. *Clin Transl Sci*, 2020. 13(6): p. 1103-1107.
65. Sahragardjoonegani, B., et al., Repurposing existing drugs for new uses: a cohort study of the frequency of FDA-granted new indication exclusivities since 1997. *Journal of Pharmaceutical Policy and Practice*, 2021. 14(1): p. 3.
66. Drew, A. Gaining New Indications With Real World Data: The 505(b)(2) Sweet Spot. 2017; Available from: <https://premierconsulting.com/resources/blog/gaining-new-indications-with-real-world-data-the-505b2-sweet-spot/>.
67. Tanaka, S., et al., Real-world evidence of raloxifene versus alendronate in preventing non-vertebral fractures in Japanese women with osteoporosis: retrospective analysis of a hospital claims database. *J Bone Miner Metab*, 2018. 36(1): p. 87-94.
68. Prescription-to-Nonprescription (Rx-to-OTC) Switches, USFDA, Editor. 2022: The United State.
69. Stewart, M. Harness the spirit of experimentation to maximize RWE potential for OTC. 2021; Available from: <https://www.iqvia.com/blogs/2021/12/harness-the-spirit-of-experimentation-to-maximize-rwe-potential-for-otc>.
70. Wong, C.K.H., et al., Real-world effectiveness of molnupiravir and nirmatrelvir plus ritonavir against mortality, hospitalisation, and in-hospital outcomes among community-dwelling, ambulatory patients with confirmed SARS-CoV-2 infection during the omicron wave in Hong Kong: an observational study. *Lancet*, 2022. 400(10359): p. 1213-1222.
71. Electronic Health Record Sharing System, in Cap 625. 2015: HKSAR Government.
72. Henry Yau, C.W. Clinical Research Management and Compliance at Study Site. 2015; Available from: https://www.med.hku.hk/images/document/04research/institution/ha_handbook_on_Clinical_Research.pdf.
73. Kenny Shui, A.T. How Hong Kong can build on its strengths to become a global biotech data hub. 2022; Available from: <https://www.ourhkfoundation.org.hk/en/report/32/science-tech-innovation/how-hong-kong-can-build-its-strengths-become-global-biotech-data>.
74. Bastarache, L., et al., Developing real-world evidence from real-world data: Transforming raw data into analytical datasets. *Learn Health Syst*, 2022. 6(1): p. e10293.
75. Shirley V. Wang, S.S., Assessing and Interpreting Real-World Evidence Studies: Introductory Points for New Reviewers. *Clinical Pharmacology & Therapeutics*, 2021. 111(1).
76. Wang, S.V., et al., Reproducibility of real-world evidence studies using clinical practice data to inform regulatory and coverage decisions. *Nature Communications*, 2022. 13(1): p. 5126.