Real World Evidence in healthcare decision making:

Global trends and case studies from Latin America

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RWE in healthcare decision-making: Global trends and case studies from Latin America

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Abbreviations

AIFA	L'Agenzia Italiana del Farmaco
AL	Adaptive Licensing
AMNOG	Arzneimittelmarkt-Neuordnungsgesetz
ANVISA	National Sanitary Agency in Brazil
AP	Adaptive Pathways
BD4BO	Big Data for Better Outcomes
CAD	Coverage With Appropriateness Determination
CADTH	Canadian Agency for Drugs and Technologies
CDC	Center for Disease Control and Prevention
CE	European Commission
CED	Coverage With Evidence Development
CENABAST	Central de Abastecimiento
CER	Comparative Effectiveness Research
CMA	Conditional Marketing Authorization
CPRD	Clinical Practice Research Datalink
CSP	Coverage With Study Participation
CUP	Compassionate Use Programme
DES	Drug Eluting Stents
DUS	Drug utilisation studies
EAPs	Early access programs
EFPIA	European Federation of Pharmaceutical Industries and Associations
EHRs	Electronic Health records
EMA	European Medicines Agency
EMIF	European Medical Information Framework
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EPS	Health Promotion Entities

EU	European Union
FDA	Food and Drug Administration
FONASA	National Health Fund in Chile
FOSYGA	Solidarity and Guarantee Fund
G-BA	The Federal Joint Committee in Germany (Der Gemeinsame Bundesausschuss)
GP	General practitioner
HAS	Haute Autorité de Santé in France
HCPs	Healthcare Practitioners
HHS	Department of Health and Human Services in USA
HIPAA	Health Insurance Portability and Accountability Act in the United States
HITECH	Health Information Technology for Economic and Clinical Health
HRQoL	Health Related Quality Of Life
HTA	Health Technology Assessment
ICD	Implantable Cardiodefibrillator (ICD).
IMI	Innovative Medicines Initiative
IND	Investigational New Drug
IPS	Service Provider Institutions
IQWiG	Quality and Efficiency in Healthcare
ISAPREs	Health Insurance Institutions in Chile
MAES	Managed Entry Agreements
MoH	Ministry of health
NICE	National Institute for Health and Clinical Excellence
NIH	National Institutes of Health
NIS	Prospective non-interventional studies
NPPs	Named-Patient Programs
OCDE/OECD	Organisation for Economic Co-operation and Development
OIR	Only in Research
OWR	Only with research

PAES	Post-Authorisation Efficacy Studies
PAMI	Programa Atención Medica Integral in Argentina
PASS	Post-Authorisation Safety Studies
PBAC	Australia's Pharmaceutical Benefits Advisory Committee
PBRSAs	Performance-Based Risk-Sharing Agreements
PCORnet	National Patient-Centered Clinical Research Network
POS	Mandatory Health Plan in Colombia
PRO	Patient-Reported Outcome
R&D	Research and development
RCT	Randomized Controlled Trials
RWD	Real World Data
RWE	Real World Evidence
SD	Standard Deviation
SGSSS	General System of Social Security in Health in Colombia
SMC	Scottish Medicines Consortium
UK	United Kingdom
UPC	Unit of Payment per Capitation
US	United States
WHO	World Health Organization

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Executive Summary

Background

Real world evidence (RWE) is used globally to assess treatment patterns, costs and outcomes of interventions. It has become an important source of information for decision-making in the health care system, including the pharmaceutical, biotechnology and medical devices industries. In recent years, Latin America has seen a surge of interest in RWE, with increasing numbers of health economists and pharmaceutical companies seeking evidence to inform health technology assessment (HTA) decisions and best practice in the healthcare sector.

However, the data infrastructure, legal frameworks and collaborative management of databases in healthcare is often limited in Latin American countries. RWE specialists from universities in Argentina, Brazil, Chile, Colombia and ICON plc (formerly Mapi Sweden AB) met during a workshop hosted by the Novartis Oncology Latin America & Canada Market Access Regional team ("Novartis Oncology Latam Market Access Team") to discuss RWE generation in health care through collaboration, mutual understanding and establishing best practices. Bringing together academic expertise and an industry perspective, a series of workshops were held in Latin America, seeking to invite input from key stakeholders from the healthcare setting including HTA and regulatory bodies.

While the standard practices for RWE use are improving, the lack of coordination and incentives to streamline RWE generation for use in the pharmaceutical, clinical and healthcare settings, remain a challenge. This white paper is a summary of expert contributions and targeted literature review on the key opportunities and challenges for Latin American institutions, spanning both the public and private healthcare sectors.

Objectives

- To clarify basic RWE concepts, by evaluating the use of health care data on national or regional scales to form the "big data" phenomenon.
- To identify examples of the integrated generation of healthcare and economic data
- To identify examples of the uses of RWE in health systems amongst stakeholders.
- To evaluate the strengths and weaknesses of RWE uses globally
- To identify the methodological and practical challenges of integrating evidence-based practice into healthcare management
- To synthesise case study literature from health economics and epidemiologists in Argentina, Brazil, Chile and Colombia.

– To identify future directions for regulation and execution of RWE in Latin America

Methods

The white paper is an independent collection consisting of the outcomes and discussions held during a series of workshops and consultations with key opinion leaders (KOLs) in four Latin American countries in 2017 as well as the targeted literature research and contributions from the KOLs. The targeted literature review of data generation and RWE uses in both the Latin American healthcare system and internationally, was conducted by the KOLs and ICON prior to the workshop being held and this white paper being developed. Literature was evaluated with a societal angle, acknowledging a healthcare, patient, payer and industry perspective. In consultations following the Latin American workshops, information on RWE and best practices was gathered from the KOLs, who included health economists and epidemiologists in both Latin America and internationally. KOLs were asked to evaluate the generation and uses of RWE in their fields, to provide expert opinion on the strengths, weaknesses, challenges and opportunities for harnessing and applying RWE to the healthcare setting. These expert contributions form the basis of the case studies section of this white paper.

Basic concepts and generation of real-world evidence

Real-world data is captured through primary and secondary sources. Primary data is actively collected for research questions where accurate and reliable data of interest is unavailable (Gliklich et al., 2014). In routine practice settings, primary studies typically gather data on effectiveness or resource utilization. However, primary data studies can also be used to collect data on the efficacy or a treatment in clinical practice; post-Authorization Efficacy Studies (PAES) are designed to capture therapeutic efficacy and benefit-risk in a real-world setting. This includes both randomised (explanatory trials and pragmatic trials) to assess treatment efficacy, as well as observational studies to assess post-authorisation safety, benefits and effect-modifiers (Gliklich et al., 2014). These studies may either be voluntarily led or conducted based on a regulatory condition of authorisation.

Secondary data sources are defined as data collected for purposes other than the study design at hand (Gliklich et al., 2014). Secondary data can be captured through healthcare data registries and location or disease-specific databases. This white paper has identified the following secondary data sources that are used to generate RWE:

– Patient registries collected by health professionals in the real-world setting, often used as secondary data to conduct cohort studies to track the natural history of diseases and monitor safety, effectiveness and quality.

- Administrative databases capture process indicators from reimbursement, facility or insurance data, and can be used for retrospective longitudinal or cross-sectional analyses of healthcare utilization and economic impacts.
- Electronic medical records (EMRs), also collected by healthcare professionals, are patient medical charts that have been digitalised, they also used to make long-term observations;
- Health surveys capture health status, resource utilization, and expenditures;
- Surveillance systems monitor distribution and history of diseases, stimulate research and evaluate control measures or facility planning;
- Online communities can be a source for self-reported data or wearable device data.

Uses of real-world evidence

The data generated from real-world studies or databases can be used as evidence for quality improvements and best-practice management by various healthcare sector stakeholders. For instance, regulators use RWE to reduce the time to market authorisation for promising new drugs using post-approval safety studies or early-access programs, for monitoring and evaluation of treatments outside of the clinical setting. The legal framework and application of these programs vary according to the healthcare system context, but are generally aimed to meet the needs of patients suffering from a rare or highly-debilitating disease.

Real-world evidence is often used to complement randomised controlled trial (RCT) data in HTA submissions. While RCT evidence is critical, RWE can enhance decision-making on whether to reimburse and with what conditions. Data on real-life costs and effectiveness of treatments in practice is a necessary complement to the clinical data. Conditional reimbursements can also be granted for treatments that require further data collection in the real-world environment. These reimbursement practices operate in various healthcare systems such as Germany, the UK, Australia and others (Carbonneil et al., 2009, Claxton et al., 2012, Walker et al., 2012).

Clinicians and healthcare practitioners use RWE to inform best-practice guidelines and value assessment frameworks. Using evidence from real-world settings, the frameworks can incorporate the overall patient experience as well as costs and quality of life. In addition, data enables healthcare researchers to identify specific subpopulations that are most applicable for clinical trials, and demonstrates how cost-savings can be achieved.

RWE has the potential to support safe and timely access to medicines, a key requirement for patients with unmet needs, such as those with chronic, rare or irreversibly progressing rare diseases. The systematic involvement of patients and their advocates in product

development is an opportunity to enlist patient support for the secondary use of health data (or the setting up of registries) to enhance evidence generation beyond authorisation. Early product entry in niche indications typically require high-quality patient registries to collect effectiveness, safety and HTA information.

The pharmaceutical industry uses RWE in various phases of product development. Initially, it is captured and used to design efficient trials, to identify underserved patient populations, develop therapies for unmet needs, and assess available therapies in real-world use. Fundamentally, RWE enables the pharmaceutical industry to identify and work with defined homogenous populations, rather than aiming to meet the needs of heterogeneous populations.

Case studies: Argentina, Brazil, Chile, and Colombia

The main findings of KOL consultations in Argentina show fragmented database management and sporadic uses of RWE in HTA decisions. While independently-managed providers do routinely capture data, there is not yet a framework in place to coordinate between databases, share findings or make linkages at regional or national levels. This results in the limited generalizability and transferability of RWE in Argentina.

Brazil's main findings demonstrate an increasing interest in RWE for patient-reported outcomes (PROs) and the cost-effectiveness of interventions. Given a heightened awareness of the scarcity of resources, health economics is an increasingly acknowledged field. Brazil has a comprehensive national health information system, DATASUS, as well as extensive national health surveillance and pharmacovigilance systems. However, access to RWE in Brazil is limited by the lack of continuous patient data, inconsistencies in common indicators and variation in data quality and security.

The generation of RWE in Chile is supported by national data-collection systems, well-executed registries, and the systematic monitoring of patients' safety after treatment authorizations. However, the uses of RWE are limited by a lack of longitudinal data, scarce funding for registry data research, and a lack of championship from the MoH. However, Chile expects to see coordination between public and private institutions to activate funding for the development of RWE research in the future.

The Colombian registry system has been capturing national real-world health data for decades, demonstrating a well-established and integrated governance model. Health economists have been able to generate evidence from the epidemiological, clinical and cost data by producing simulation models or budget impact analysis. Despite insufficient human resources and capacity, Colombia has profited from access to longitudinal data and a history of evidence based health decision-making.

Limitations

Limitations to this white paper are as follows. First, country-specific expert opinion was sought for each case study, resulting in some inconsistencies in the focus and depth of topics evaluated in the countries. It should also be noted that since the time of contribution submissions and writing (June-October 2017), there may have been updates and changes in the use, laws or regulations of RWE. There is a targeted, rather than systematic, approach to the consolidation of information on RWE given the lack of literature and the use of non-published or grey literature. Finally, the pitfalls of comparing Latin American health care systems to European and American should be highlighted. While no direct country-comparison is possible, the funding mechanisms, epidemiological profile and basic structure of Latin American health systems are often distinct to the single-payer systems in Europe or the largely private health insurance-reliant US system.

Conclusion

This paper clarifies the basic concepts of RWE in healthcare systems, and the tools needed to generate RWE in a Latin American setting. It identifies uses of RWE in cost-saving exercises such as targeted clinical trial designs by pharmaceutical companies, and conditional reimbursement strategies by payers. It also identifies the strengths and weaknesses of RWE generation and uses in four Latin American countries via case studies, summarising the key challenges and opportunities for healthcare system-specific integration.

The main findings show that Latin America has comprehensive databases, albeit often fragmented and sporadically managed. There is also wide-ranging use of RWE in HTA submissions, and expertise to analyse the supporting data, but at the time of writing RWE from the region is not consistently captured at a national level. Findings show that regulation and pharmacovigilance from regulatory agents as well as patients and clinicians may trigger increased levels of safety and effectiveness monitoring. However, collaboration between databases and registries are essential for large, representative samples. Recommendations for future research include monitoring and evaluating the uses of digital databases, the standardisation of hospital registry data and encoding standardised data privacy legislation. By exploring the best practices for data generation and management, researchers can support access to aggregated and transferrable healthcare data within Latin American region and countries, enhancing the health product-authorisation process.

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1.0 Introduction

The use of real world evidence (RWE) to assess treatment patterns, costs and outcomes of interventions has become an important source of information for decision-making among stakeholders of the health care system, including the pharmaceutical, biotechnology and medical device industries. The role of RWE is crucial in supporting value assessments of often high-cost treatments, informing decisions on innovative access schemes, identifying subpopulations for whom outcomes are markedly better or worse, and optimizing investment and budget allocations.

Multiple initiatives across the world highlight the role that RWE plays as a valuable complement to the evidence generated in traditional randomised controlled studies.

In Europe, these initiatives include the strengthening of the European Union's (EU) legal and standard practice frameworks for pharmacovigilance and subsequent deployment of registries with extended mandates; the creation and extension of the European Medicines Agency (EMA) Adaptive Pathways process with the subsequent request to generate and use RWE in early phase medicinal production; the Innovative Medicines Initiative's (IMI) project largest public-private partnership between the European Commission (CE) and the European Federation of Pharmaceutical Industries and Associations (EFPIA), which aims to improve the drug development process by supporting efficient discovery and development of safer medicines. Some schemes worth mentioning are the Big Data for Better Outcomes (BD4BO) programme, the European Medical Information Framework (EMIF) Programme and IMI GetReal.

Since the United States (US) adopted the Safety Innovations Act in 2012, the Food and Drug Administration (FDA) encourages the use of RWE for the follow-up of new healthcare technologies introduced under Priority Review, Breakthrough Therapy, Accelerated Approval, or Fast Track. Further, the 21st Century Cures Act (enacted in December 2016) expedites the approval process for new drugs and devices by easing the FDA requirements for new products or new indications on existing drug. The act also allows for sponsors to provide "data summaries" and RWE (observational studies, insurance claims data, patient input) rather than full clinical trial results (Franz, 2016, Jacoby, 2016, KAPLAN, 2016).

Consequently, Latin America is witnessing a surge of interest for this type of evidence, and pharmaceutical companies are at the forefront of these developments, raising awareness, fostering dialogue and launching initiatives.

During the second half of 2016, ICON plc (formerly Mapi Sweden AB) and the Novartis Oncology Latam team, together with a wealth of regional academic institutions, made significant strides in this direction by launching projects in Argentina, Brazil, Chile, and Colombia. With workshops that engaged local key opinion leaders (KOLs), dialogue was facilitated amongst government officials, healthcare providers, payers, and other

stakeholders on the challenges, opportunities and applications of RWE. The objectives were to create a collective understanding around basic definitions, the use of RWE in regulatory decisions and Health Technology Assessments (HTA), the legal and operational considerations and the typical requirements in the generation, consolidation and use of RWE. Learnings from international experiences were shared and country-specific insights were provided by local experts.

The main goal of this White Paper is to disseminate and publicize the findings of the research presentations delivered during the workshops of reference as well as foster good practices in the generation and use of RWE in healthcare decision-making in Latin America.

This White Paper is organized as follows. Section 2 gives a brief overview of RWE generation and basic concepts. The third section examines opportunities offered to all participating stakeholders. Challenges and hurdles are outlined in Section 4. In the fifth section, four case studies in Latin America are presented. Lastly, overall results are discussed, followed by our conclusions. The closing section discusses RWE in Latin America and globally, including limitations, action plans, future research and possible collaborations.

2.0 Real World Evidence basic concepts

2.1 Big data in healthcare

The digital revolution and information society in healthcare has opened new opportunities to explore and analyse substantial amounts of data for different purposes from a wide variety of sources. The amount of health-related data is growing exponentially, from basic science to clinically based genomics and personalized medicine, and continues to evolve at both the population and the individual levels. Accordingly, the literature on Big Data in Healthcare is propagating. Thus, we shall start by clarifying three basic closely related yet somewhat different concepts:

- "Big data" is a blanket term for any collection of data sets too large and complex to process using traditional data processing applications. Defined by the Oxford English Dictionary as extremely large data sets that may be analysed computationally to reveal patterns, trends, and associations, especially relating to human behaviour and interactions
  (Oxford Dictionaries).
- "Real World Data" (RWD) in health is considered "big data" because of its diversity and complexity even when its volume varies (depending on the combination of multiple sources), but the definition we are adopting in this paper is data used for decision-making that are not collected in conventional randomized controlled trials (RCTs) (ISPOR Task Force, 2013).
- "Real-World Evidence" (RWE) is the evidence derived from aggregation and analysis of RWD elements (FDA, 2016). As such, patient-level data contained in one dataset or linking more than one, is analysed to answer questions structured in a scientifically meaningful way to influence research and development (R&D), clinical, and commercial decisions. The central notion is that "data" conjures the idea of simple 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 are raw materials and alone are non-informative (ISPOR Task Force, 2013).

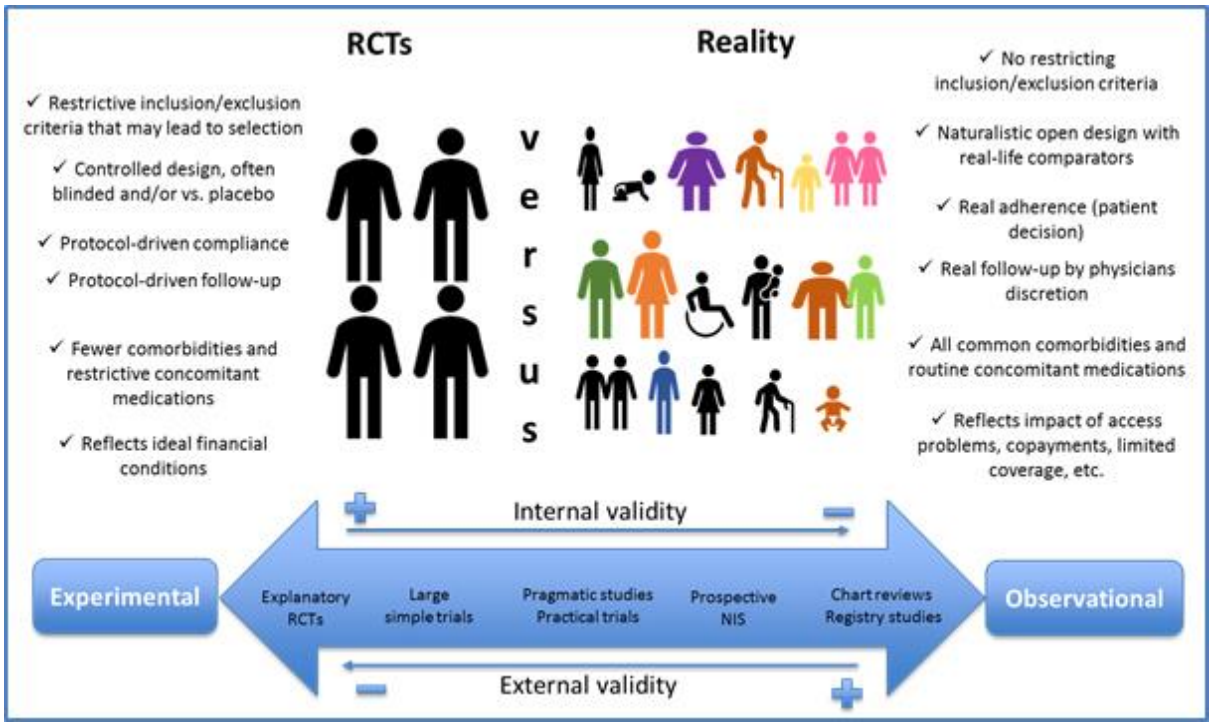
2.2 Experimental and Observational studies

Given that the contrast between RWE and the evidence generated in conventional RCTs is central to our definition, we shall consider these differences. Figure 1 presents schematically this contrast on which we further elaborate in this section.

The first and fundamental difference in the generation of the evidence resides in the two opposite types of study designs: experimental studies and observational studies. In experimental studies, the researcher intervenes by manipulating the variable of interest. The best-known example is the RCT. In observational studies, the researcher does not intervene and reports observed differences between subjects that already differ in the variable of interest (Jepsen et al., 2004, Petrie and Sabin, 2005, Gosall and Gosall, 2006).

Historically, academic institutions such as the Cochrane Collaboration have established a hierarchical ranking of the evidence based on research design strength (Higgins and Green, 2011, Evans, 2003). Typically, data from RCTs are at the top of the hierarchy, followed by data from non-randomized intervention studies, observational studies and so forth (Woolf, 2000). Ranking evidence based on research design rigour, however, does not provide a complete picture of the appropriateness of RWE to address certain research needs. For example, the results from many RCTs are focused on a very specific group of patients and thus, the results are not always generalizable to a broader population. Conversely, a well-conducted observational study may be highly useful in certain situations, provided that potential biases have been adequately addressed. Indeed, some would argue that observational data can often provide more relevant evidence for patient outcomes in actual clinical practice than a registration RCT (ISPOR Task Force, 2013).

Figure 1: Experimental versus observational research



RCTs are considered to be more reliable than observational studies when evaluating the efficacy of treatments. However, meta-analyses comparing the results of different intervention typologies from both types of studies did not yield significant differences in the

estimates of the effects (Ioannidis and Lau, 2001, Concato et al., 2000, Benson and Hartz 2000). Also, observational studies can be used to reduce the uncertainty of product safety, by monitoring the risk of adverse events in routine care, rather than in the controlled environment of clinical studies.

Some of the constituting elements of RCTs such as their prospective design, pre-specified well-defined endpoints, randomization and control groups, and blinding, provide unbiased measures of impact in the trial population. However, these advantages could be perceived as disadvantages, as a study design that increases internal validity can limit the external validity and generalizability of findings. This creates uncertainty over which interventions are better suited for different settings with different populations (ISPOR Task Force, 2013).

Conversely, observational studies are often the best method for determining the natural history of disease or measures of occurrence (incidence, prevalence) and present several advantages such as allowing for multiple outcome records, being less costly compared to RCTs, avoiding the ethical problem of experimental exposure to risk factors and offer the ideal setting for generating hypotheses. Additionally, observational studies provide results on a broader range of outcomes (e.g., PROs, HRQoL, and symptoms) than have traditionally been collected in RCTs (i.e., major morbidity and short-term mortality).

RWE generation is a necessary complement to experimental research. In fact, as we depict in Figure 1, RWE in health can be generated through a continuum of study designs, from randomized pragmatic clinical trials on one end to claims databases or medical chart review studies at the other. The results obtained from all study designs should be interpreted with consideration of population confounders in both treatment arms, and the method used to assess outcomes given the potential limitations of the study (ISPOR Task Force, 2013, Kent, 2011). Although it is important to understand the strengths and limitations of both RCTs (efficacy studies) and observational studies (effectiveness studies), none of the study designs should be considered in isolation since all types of evidence rely primarily on the rigour with which individual studies were conducted (regardless of the methodological approach) and the care with which they are interpreted (Berger et al., 2012). Interpretation of RCT and observational study results can help establish the efficacy/effectiveness and safety of a therapeutic option.

2.3 Generation of real world evidence

RWE can be generated or collected from multiple resources. These resources can be grouped into primary (actively collecting new data) and secondary (analysis of existing data sources).

2.3.1 Primary (actively collecting new data)

Table 1 below summarises primary data collection studies that generate RWE for the efficacy, effectiveness or costs of interventions. Each of the four study designs are summarised in the table, along with the typical uses of the RWE generated, and the patient population the study may be used with. The advantages and disadvantages to using each data collection type compared to others has also been considered. It should be noted that the data collection types are broadly classified, so a certain level of overlap remains.

Table 1: Summary table for primary-data collection

Type of RWE derived from purposely-collected primary data	Study design and use	Advantages	Disadvantages
Randomized PAES (pragmatic trials)	– Randomized trials conducted post-approval in real-world conditions (European Medicines Agency, 2016) – Measure effectiveness outcomes and/or associated treatment costs – Conducted in routine practice settings – Compare alternative clinical interventions – Heterogeneous participants and practice settings (Tunis et al., 2003) – Cost and effectiveness data are used by policy makers for evidence-informed decisions on treatment choices	– Mimics real-world circumstances – Reflects real patient variations – Easily transferable to policy making arena – meets reimbursement board's requirements. – Evidence from real life settings can be used to inform funding, regulation, policy and organizational changes – (Kowalski and Mrdjenovich, 2013)	– Must have a large enough sample sized to detect clinically significant effects. – Can be costly to recruit and monitor a large and diverse group of patients
Non-randomized PAES (Non-interventional studies)	– Observational studies conducted post-approval – No interference in hospital standard practices – Predominantly observational study designs, but regulations differ per country (Chalkidou et al., 2012)	– Non- interference in patient treatments means study design is less costly than alternatives – Patients are selected a priori, reducing risk of bias compared to retrospective studies	– Unknown risk of bias since in the study cannot intervene in the sampling or treatment plan of the hospital.
Post-authorisation safety studies (PASS)	– Can either be clinical or l or non-interventional studies conducted on post-authorization treatments – To measure the effectiveness of risk-management by investigating potential or identified risks – To assess patterns of drug utilisation that may affect medicine safety – May be voluntarily conducted or imposed by regulatory committees – Further details can be found under heading 3.1.1	– Conducted in real-life setting – Study design assistance available from EMA and other regulators – Ensures that thorough safety information is available for dissemination amongst providers	– Risk of bias remains, especially deriving from channelling – Highly regulated, thus can be costly to monitor
PROs and other surveys	– Effects of health condition and/or treatment reports direct from patients, proxies or caregivers – Include details on symptoms, functional status, HRQoL, treatment satisfaction, preference and adherence. – Gives patient's perspective on outcomes related to treatments or policies.	– Widely used by decision-makers – Help to assess the impact of emerging treatments – Communicate the benefits of treatments in label and promotional claims (ISPOR Task Force, 2013)	– Instruments need validation and cultural adaptation – Diverse methodological challenges (e.g. potential recall bias or informative missing data in longitudinal design)

NIS: Non-interventional Studies; PAES: Post-Authorisation Efficacy Studies; PASS: Post-Authorisation Safety Studies; PROs: Patient-reported Outcomes;

2.3.2 Secondary (analysis of existing real-world data)

Table 2 below summarises secondary data collection studies that can generate RWE based on routine data collection in sources such clinical registries, medical histories or administrative databases. Like primary data collection, the RWE generated from secondary sources can be analysed to identify the cost-effectiveness or efficacy of interventions. Each of the six study designs are summarised in the table, along with the typical uses of the RWE generated. The advantages and disadvantages to using each data collection method compared to others has also been considered. Certain overlap between these categories may remain.

Table 2: Summary of secondary use of existing real-world data

Type of RWE derived from secondary use of existing data	Study design and use	Advantages	Disadvantages
Clinical / Patient Registries (known as quality registers)	– Observational cohort studies for disease or treatment groups. – Used for understanding natural history of diseases – To monitor safety and effectiveness, care quality, provider performance, cost-effectiveness (ISPOR Task Force, 2013)	– Captures real-time data – Large and diverse population groups that reflect management practices and outcomes. – Long-term outcomes can be assessed (ISPOR Task Force, 2013)	– Patient allocations are not randomized, meaning effectiveness estimations can be biased
Administrative databases	– Usually collected for reimbursement, facilities management and to record procedures are charged – for e.g. claims data. – Retrospective longitudinal or cross-sectional analyses – Used for assessing the economic impact of interventions, and the associations between them and outcomes	– Generally low-cost and quick to conduct. – Large databases allow for easy identification of patients with rare events and assessment of economic impact of interventions (ISPOR Task Force, 2013) – Reflect professional routine care, major clinical endpoints, utilization and costs	– Endpoint adjudication is not always feasible; not always possible to systematically assess clinical conditions. – Do not report PROs. (Schneeweiss et al., 2016)
Electronic medical history/records and chart reviews	– Record, clinical events, laboratory results and treatment histories. – On-site real-time clinical research can be made for long-term observations	– Progress in time to researcher access and medical database linkages. – Possible to reach patients for additional information	– Data is frequently missing – No systematic assessment of conditions. – Limited use of PROs.
Health surveys	– Collect data from patients, target groups or public – Survey respondents on health status, wellbeing, resource utilization, demographic, health care expenditures and lifestyle data – Administered at both national and regional levels	– Seek to survey representative target groups – Methodologically rigorous	– Typically lack granularity in clinical data
Data generated by surveillance systems	– Used to survey distribution of illnesses and natural history of diseases – Also, used to generate hypotheses, stimulate research, evaluate control measures and monitor changes, and facilitate planning – Surveillance conducted through notifiable diseases, laboratory specimens, vital records, sentinel surveillance, registries, surveys,	– Constantly monitored “fresh” data, so prompt action can be taken if needed. – Particularly responsive to acute diseases such as injections and injuries	– Typically, they lack granularity and specific clinical variables (such as biomarkers, comorbidities, performance status, etc) as well as resource utilization and cost, are often missing – Not always provide with longitudinal patient-specific follow-up, but rather aggregated data year on year

	and administrative data systems (Institute of Medicine (US) Committee on a National Surveillance System for Cardiovascular and Select Chronic Diseases, 2011) – Center for Disease Control (US) defines public health surveillance as ongoing, systematic and regarding health-related events for use in public health action to reduce morbidity and mortality (German et al., 2001).		
Online communities/ repositories	– Self-reported data from online communities, wearable devices and eHealth databases. – Social media is a potential source of RWE as patients can log in and update their records	– Possible to link de-identifiable data across other sources of 'Big Data' – A new area with potential for new innovative study designs	– Maintaining non-identifiable nature of the data is not guaranteed given that this is a new and unregulated area

2.3.3 What are the pros and cons of each study design?

Identifying the most appropriate choice of study design and analytic strategy requires expertise and unavoidably entails trade-offs. When evaluating the suitability of study designs to approximate a counterfactual experience in patients who did not participate in a trial, it is often best practice to combine methodological approaches. A perfect solution to generating evidence is rarely possible in a single study regardless of whether it is a database analysis or not (Schneeweiss et al., 2016). For instance, it is possible to combine study designs by pairing baseline randomization with observational data. This dilemma is reflected in guideline documents that share a non-prescriptive attitude towards design and analytic choices (The International Society of pharmacoepidemiology, 2008, Johnson et al., 2009, European Medicines Agency, 2016).

Table 3 provides a non-exhaustive overview of the pros and cons of randomised to non-randomised study designs, adapted from the ISPOR Value and Outcome Spotlight (Eichmann, 2015). While study designs are typically determined by the existing data available, budget and research questions, Table 3 shows the coverage of quality that can be expected from study designs depending on the practical and methodological considerations. A double plus (++) represents excellent, a single plus (+) represents good, and a minus (-) represents less adequate coverage of quality.

Table 3: RWE study designs, practical and methodological considerations

Practical and methodological considerations	Randomised studies (RCTs and pragmatic studies)	Prospective observational studies/ Registries	Databases (administrated)	Retrospective chart review
Comparison validity	++ Causality	+ Association	+ Association	+ Association
Internal validity (Carlson and Morrison, 2009)	++ Lower probability of Systematic error	- Confounding factors	- Confounding factors	- Confounding factors
External validity (Carlson and Morrison, 2009)	- Lower generalizability	++ Higher generalizability	++ Higher generalizability	++ Higher generalizability
Need to measure small difference in outcomes	++ High precision	- Low precision	+ Moderate precision	- Low precision
Long-term data that can identify trends over time	- High attrition rates	++ HCP dependent	++ Dependent on HCP / database	+ HCP dependent
Study sample and epidemiological validity	- Usually biased	++ Assuming defined sampling process	+ Depending on coverage	+ Depending on coverage
Randomization is restricted because of ethical considerations	- Randomization required	++ No randomization requirements	++ No randomization requirements	+ Sample selection may be randomized (not the allocation of the intervention)*
Outcomes of interest collected directly from patients (PROs)	- PROs may be subject to selection bias	++ PROs	++ PROs	++ PROs
There are no sufficient historical data to conduct retrospective analysis	++ Primary data collection	++ Primary data collection	- Secondary data analysis	- Secondary data analysis
Limited budget; it is not feasible to conduct a resource-intensive study	- Most expensive	+	++ Cheapest	+
The study results are needed quickly	- Slow	+ Quicker	++ Quickest	+ Quicker
Data is required for several countries	+ Transferrable across countries within the same trial population	- Influenced by health care system	- Least generalizable across countries	- Influenced by health care system

Source: Adapted from adapted from ISPOR value & outcome Spotlight (Eichmann, 2015)

* Dependent on research question and regulatory environment

HCP: Healthcare providers; PROs: Patient-reported outcomes; RCT: randomized controlled trials

Finally, it is important to consider the time and resources required for the planning and execution of study designs. RWE studies typically involve a wide range of stakeholders, including health professions, health care institutions such as hospitals and technology manufacturers. Generally, it is harder to secure an alignment of interests to conduct a prospective randomised study than a prospective observational study. Therefore, randomised RWE studies tend to be reserved for situations where it is imperative to obtain unbiased estimates of treatment effect. If the objective is merely to obtain long term data on outcomes or costs, or to explore in more detail the effects of an existing proven technology in sub-groups of the patient population, an observational study may suffice.

In situations where treatment effect needs to be established, but agreement cannot be reached through a randomised study, it is important to collect information on patient characteristics (e.g. level of risk, previous medical history) so that these can be used as covariates in any subsequent analyses of observational studies.

The other major consideration is the time and resources to conduct the study, whether a randomised or an observational study. To this end, it is always worth checking whether there are any existing datasets that could be analysed, since this is likely to be the quickest and least expensive option. If a prospective study is required, consideration should be given to the maximum length of time to conduct the study. Unlike the studies undertaken prior to the launch of a drug or other health technology, RWE studies are usually undertaken to answer a policy question that may be time-sensitive. Therefore, it is important to have alignment between the time to execute the study and the time results are required.

3.0 Opportunities offered by RWE from a multi-stakeholder perspective

RWE research is an increasingly major component of biopharmaceutical product safety, development and commercialisation, from the industry, patient and regulator perspectives. RWE has a significant impact on the reimbursement and utilization of new products. There are multiple parties driving decisions: regulators, public and private payers, prescribers and patients. All parties seek to better understand the impact of a new product in a real-world setting. This interaction results in RWE generation being included earlier in the research and development phase.

3.1 For regulators

Over the past ten years a heightened interest in improving timely access for patients to new medicines was observed.

On the one hand, the European Medicines Agency (EMA) started introducing regulatory processes aimed at cutting down lead-time for marketing authorization in indications with high unmet medical needs. They introduced initiatives such as the Compassionate Use Programs (based on Regulation (EC) No 726/2004) (European Union, 2004), the Conditional Approval Mechanism (based on Regulation (EC) No 507/2006) (European Union, 2006), and the Initiative for Patient Registries launched in September 2015.

On the other hand, the United States FDA developed four approaches, which were formalized with the adoption of FDA Safety Innovations Act in 2012. They are known as Priority Review, Breakthrough Therapy, Accelerated Approval, and Fast Track. Additionally, in December 2016 the 21st Century Cures Act that was enacted into law to describe the amendment of the Federal Food, Drug, and Cosmetic Act by inserting, amongst other things, a provision to assess the potential for use of RWE in drug marketing-approval programs.

These initiatives require sound RWE and we will describe the most salient elements in this respect.

3.1.1 Pharmacovigilance

Following the regulatory requirement for early detection in safety and tolerance of newly-authorised drugs, the following real-world study designs were established.

3.1.1.1 Post Approval Safety Studies

Post approval safety studies (PASSs) are carried out after a medicine has been authorised and aims to obtain further information on safety, or to measure the effectiveness of risk-minimization measures. PASS can either be clinical trials or non-interventional studies

(EMA, 2013). The key PASS characteristics are summarised in **Error! Reference source ot found.**.

A PASS may be initiated, managed or financed by a marketing-authorisation holder voluntarily or be imposed, in which case it is compulsory. For example, in Europe, these include studies that are a specific obligation for a marketing authorisation granted under exceptional circumstances and other studies that the Pharmacovigilance Risk Assessment Committee (PRAC) requests the company carry out. Voluntary PASSs are sponsored or conducted by MAHs on their own initiative. They include non-imposed studies that are requested in risk-management plans.

In July 2015, EMA launched a 12-month pilot to encourage companies to seek scientific advice for PASSs for medicines. A PASS is defined as any study relating to an authorised medicinal product conducted with the aim of identifying, characterising or quantifying a safety hazard, confirming the safety profile of the medicinal product, or measuring the effectiveness of risk management measures. This voluntary optional procedure helped improve the design of studies intended to collect further information on a medicine's safety post-launch (EMA, 2013). The program is still in use and has an increasing number of protocol applications every year (Engel and Almas, 2016).

3.1.1.2 Drug utilisation studies

Drug utilisation studies (DUS) examine the marketing, distribution, prescription and use of drugs in a society, with special emphasis on the resulting medical, social and economic consequences (WHO, 2003).

A DUS describes how a medicinal product is prescribed and used in routine clinical practice. In particular, large populations of elderly, children or pregnant women. Patients with specific dysfunctions or concomitant conditions who are often excluded from patient populations in randomized clinical trials. Stratification by age, gender, concomitant medication and other characteristics allows a comprehensive characterization of treated patients, including the distribution of those factors that may influence clinical, social, and economic outcomes. From these studies, denominator (population at risk) data may be derived for use in determining rates of adverse reactions. DUS have been used to describe the effect of regulatory actions and media attention on the use of medicinal products, as well as to develop estimates of the economic burden of adverse reactions. DUS can provide valuable information and may be used to examine the relationship between recommended and actual clinical practice. Furthermore, these studies may help to monitor use in everyday medical practice and medication error and to determine whether a medicinal product has potential for abuse by examining whether patients are taking escalating dose regimens or whether there is evidence of inappropriate repeat prescribing (as per Appendix 1 of EMA GVP Module VIII –

July 2012 (EMA, 2016b)). Additionally, DUS detect off-label use patterns and may inform research on potential label extensions.

3.1.2 Early Access Programs and Expanded Access Process

Early access programs (EAPs) represent a unique opportunity to gather RWE, and are sometimes the first opportunity to do so outside of the controlled environment of a clinical trial setting. They include a cohort of patients receiving the same treatment indifferent regions. Globally, the programs are known as early access programs in Europe, expanded access process in the US and Special Access programs in Canada (SAP).

These programs are adopted by an increasing number of pharma companies due to several benefits offered; chiefly ethical, compliant, and controlled mechanisms of access to investigational drugs outside of the clinical trial space and before the commercial launch of the drug, to patients with life-threatening diseases having no treatment options available (Patil, 2016). EAPs can describe real-life safety data in a more diverse population (clinically, ethnically and demographically) as compared to patients fulfilling eligibility criteria in clinical trials. The information can provide insights on the effects of wider use of the drug by different patient subtypes (Estcourt, 2014).

3.1.2.1 Early access programs in Europe

In Europe there are two main types of EAPs; Compassionate Use Programs (CUPs) and Named-Patient Programs (NPPs). Both differ in certain ways within the EU and from typical Expanded Access Programs in the US, but following are the key elements.

3.1.2.1.A Compassionate use programmes

In the European Union, the EMA defines "compassionate use" as a treatment option that allows the use of an unauthorized medicinal product if under development (European Medicines Agency, 2007). Compassionate use programs (CUPs) are governed individually by EU member states. A review of CUPs in the EU indicates pre-launch access to investigational drugs, biologics and medical devices not yet authorized in the country, without considering any inclusion or exclusion criteria (Balasubramanian et al., 2016). However, CUPs enrol patients as per the laws and regulations outlined for the program, typically that the patient is suffering from a life threatening or debilitating disease, has exhausted all viable licensed treatment options and is unable to access a clinical trial (Patil, 2016). Although CUPs cannot replace clinical trial safety and efficacy data, the EMA states that evidence can be provided either as phase III trial data, or phase II trial data plus early data from exploratory trials (EMA, 2007). A recent international example of CUP use was the experimental interventions on Ebola patients, which were condoned by the WHO, conditional on the collection of efficacy evidence (World Health Organization, 2014). In this way, CUPs

can generate early insights on the safety and efficacy of treatments in a “real world” environment, as well as fulfilling unmet needs (European Medicines Agency, 2007).

3.1.2.1.B Named-Patient Programs (NPPs)

NPPs (also known as named-patient supply) provide controlled, pre-approval access to drugs in response to requests by physicians on behalf of specific, or “named”, patients before those medicines are licensed in the patient’s home country. Early access through NPPs should not be confused with CUPs as in the former, doctors obtain medicines directly from manufacturers before on an individual basis under their sole responsibility, and the EMA does not need to be informed. Yet, in the Guidelines on Good Pharmacovigilance Practices (EMA/816292/2011 and ulterior revisions), data generated in NPPs is to be included in the Periodic Update Safety Reports (PSURs). Furthermore, in some cases, following EMA’s refusal of marketing authorization, patients who derived clinical benefit from the rejected treatment may continue to receive it under NPPs, also allowing to explore subgroups for which data on long term outcomes can be collected.

3.1.2.2 EAPs in the US

In 1987 the new FDA regulations for Investigational New Drugs (INDs) were revised to provide access for a broad patient population under treatment with INDs outside of a clinical trial. In a new reform in August 2009, the FDA extended the concept and mentioned that sponsor companies conducting EAPs ought to provide information on adverse events. This information must be incorporated in IND annual reports and safety reports and that the new drug application must at least cover the summary of the expanded access exposure to the patients. With regards to the use of the data obtained from the expanded access, FDA clearly mentions that the data can be useful in assessing drugs safety profile (U.S. Government, 2009).

In further adjustments to the EAP FDA regulations, requirements for submission are defined in four categories: Treatment IND, Intermediate Size Population IND, Emergency Individual Patient IND, and Individual Patient IND. Whereas the first category (closer to the European CUPs) allows physicians to offer the drug to several patients who fulfil the criteria and are commercially sponsored; the last (closer to the European NPPs) are limited to the requested named patient or patients only and entirely initiated by physicians, who also bear liability.

European and U.S. approaches are summarised in Table 3. In both European countries and the US, EAPs can be initiated by the pharmaceutical company and physicians, but they vary in terms of liabilities and costs.

Table 4: Comparison of EAPs in the US to CUP and NPP in the EU

Criteria	EAP (US)	CUP (EU)	NPP (EU)

Legislation in place	– Expanded Access Programs (FDA, 1997)	– Article 83 (1) of Regulation (EC) No 726/2004	– Article 5 of Directive 2001/83/EC
Who initiates the program?	– Manufacturer – Physicians	– Manufacturer/Group of physicians (e.g. in Italy)	– Physicians
Criteria to define/select target population is set by…	– Manufacturer/FDA	– Manufacturer/CHMP	– Manufacturer/ Physician
Who can benefit from program? Limitation in use?	– Group of patients (treatment INDs & treatment protocols) – Named patients (single patient INDs)	– Group of patients i.e. more than one (permission is granted to a clinic or hospital as opposed to a particular patient)	– Only named patients for whom physician has made a request
Liability	– Manufacturer	– Manufacturer	– Prescribing physician
Medical product should be undergoing clinical trials or awaiting market authorization?	✔	✔	✖
Is off-label use permitted?	✖	✖	✔
Are physicians paid for taking part in the program?	✔	✖	✔
Are drugs in program prices?	✖	✖	✔ (possible)

Source: (Yazdani and Boggio)

Data collected from these access programs can be used to formulate patient-centric approaches to treatment. As per the study published in British Journal of Urology International, the data generated from access programs in the US and the UK was used to decide treatment approach to various patient subtypes suffering from renal cell carcinoma (Patil, 2016). More than 50 notifications of compassionate use programmes have been submitted to the EMA by Member States since 2006.

3.1.2.3 EAPs in Latin America

In Latin America, these types of programs exist and offer similar characteristics. In general, in the region, the regulations for EAPs, compassionate use and post-study drug delivery establish that these requests must comply with the following criteria:

I - severity and stage of disease;

II - absence of a satisfactory therapeutic alternative in the country for the clinical condition and its stages;

III - severity of the clinical picture and presence of comorbidities; and

IV - evaluation of the risk benefit ratio of the drug requested.

Table 5: Regulatory framework for EAS in Latin-American countries

Argentina	Brazil	Colombia	Chile
DISPOSICIÓN 840/1995 – Administración Nacional de Medicamentos, Alimentos y Tecnología Médica (ANMAT)	RESOLUTION - RDC NO. 38, 2013 Annex I of Administrative Rule no. 354 of ANVISA	Decreto 481-2004 Medicamento vital no disponible. INVIMA only if the case is approved by a Review Committee.	Disposiciones de la Ley N°18.164; el Decreto Supremo Nº3/2010 y la Ley N° 20.724

3.1.3 Other examples of real-world evidence use by regulators in Europe: Adaptive Pathways

RWE is crucial in balancing the trade-offs between encouraging rapid patient access to promising therapies and ensuring patients and their regulatory and physician proxies have adequate information on benefits and harms at the time of marketing authorization. The adoption of Adaptive Pathways (AP) strengthens Post-Authorisation Efficacy Studies (PAES) aiming to provide a supportive “pathway” from product development to potentially early access. APs foster early dialogue with stakeholders (regulators, HTAs, payers, patients etc.) on diseases with a high unmet medical need (EMA, 2015). APs make use of existing approval tools, in particular conditional marketing authorisation, which has been in operation in the EU (EMA, 2016a) and the US (FDA, 2017).

AP reforms the existing regulatory approach. In fact, it goes beyond changes to market authorisation, instead taking a ‘lifespan’ approach that incorporates drug development and health technology appraisal. Traditionally, the product lifecycle can be divided into two distinct phases (pre- and post-authorisation). AP replaces this single (go/ no-go) market authorisation event with a process of ‘reduction of uncertainty’ alongside iterative periods of data collection and regulatory assessment. AP makes drug development a continuum with stages of regulatory approval and evidence development running parallel with marketing (Eichler et al., 2015, Eichler et al., 2012).

RWE is a key component of AP. The EMA proposes moving away from RCTs being used exclusively as the basis for regulatory decisions, instead using the ‘entire toolbox of knowledge generation’. This includes RWE data collection and studies in addition to conventional RCTs, pragmatic RCTs and observational trials. AP is part of a changing attitude to the perceived lack of “robustness” of RWE and the EMA highlights how year-on-year advancements in RWE studies are seeing them become more systematic, generate increasingly reliable data, and undergo improvements in methodology (Eichler et al., 2015).

The Eichler et al. article examines the changes in the scientific and political environment that will make adaptive licensing (AL) the preferred approach in the near future. It also discusses the environmental changes that will enable but not in themselves necessitate a transition from the traditional regulatory and coverage decision framework. We present the external influences named as “drivers of AL” and “enablers of AL” in Table 6 (Eichler et al., 2015)

Table 6: Drivers and enablers of Adaptive Licensing (adaptive pathways)

Drivers of adaptive licensing	Enablers of adaptive licensing
– Patient expectations: demand for timely access and emphasis on unmet medical need – Emerging science: fragmentation of treatment populations and early disease interception – Healthcare systems under pressure: rise of payer influence – Pharma/investors under pressure: sustainability of drug development	– Improved understanding of disease processes, better knowledge management – Innovative clinical trial designs – Rapid learning systems in the healthcare environment – Bringing patients to the table: understanding acceptable uncertainty – From prediction to monitoring – Targeted prescribing

3.1.4 Other examples of real-world evidence use by regulators in the US: Expedited Programs

Similar to EMA's AP, the FDA has created four expedited development and review programs for serious conditions drugs and biologics. These include fast track designation, breakthrough therapy designation, accelerated approval, and priority review designation. These differ in terms of qualifying criteria, timing for request submission and for FDA response, features and consequences but they all contemplate RWE as a necessary support to document the unmet clinical need, or the effectiveness of the standard of care (SOC) over which the new therapy has the potential to offer substantial improvement, or meaningful safety advantage over SOC, etc. Additionally, the FDA sometimes uses RWE for natural history studies and retrospective observational studies to support drug approvals for rare or life-threatening diseases (Mezher, 2016). Several efforts, including the National Institutes of Health (NIH) collaboration, National Patient-Centred Clinical Research Network (PCORnet) and FDA's Sentinel initiative are already working to use these data to improve clinical trial efficiency and drug safety monitoring (Mezher, 2016).

3.2 For Health Technology Assessment Agencies and payers

RCTs are considered the golden standard to generate evidence for clinical guidelines and HTA submissions. However, RWE is used to complement RCT evidence, for designing more efficient clinical trials and understanding a drug's benefit/risk profile. It also helps market access teams with economic model building and value demonstration, and understanding the market for launch planning.

Despite the potential for bias and practical limitations in data quality and availability, the use of RWE should benefit both the pharmaceutical industry and HTA agencies. HTA agencies decide whether to reimburse, or how to tier co-payments. Regulatory approval has become merely a necessary, but no longer sufficient precondition for patient access. Some payers, or HTA agencies that advise them, currently emphasize that the "full" information package about a drug's performance has to be available at the time of the first coverage decision (Kenny, 2012). However, there is growing awareness among many other payers that they, like the regulators, cannot escape the access vs. evidence conundrum. In fact, public debate

about reimbursement tends to be even more acrimonious than about licensing because the financial element is absent from regulatory decision-making. Payers are coming to recognize that the binary concept of experimental vs. medically necessary is based on a simplified view of evidence and uncertainty—and that more nuanced policy mechanisms are necessary to align with the continuous nature of strength of evidence. It is not surprising that emerging effectiveness guidelines seek to better inform payers' coverage decisions call for more granular subgroup information (Eichler et al., 2015).

Once the coverage decision has been made, payers need to take a keen interest in ensuring appropriate prescribing, a high level of patient adherence, and real-time monitoring of treatment outcomes to realize the anticipated value for money. In all of these areas, payers benefit from the use of RWE.

3.2.1 Health Technology Assessments and Health Economic Evaluations

Observational studies examine how existing medicines and treatments are working in the health care system. As RCTs are not able to provide all information required to have a fully functional cost-effectiveness and budget impact models, these evidence gaps usually are filled with observational data. This type of study can provide information on the epidemiology of the disease, standard of care and treatment patterns, resource use, utilities (from validated PROs), indirect cost (where applicable), actual comparators, etc.

Liden et al. evaluated decisions of HTA agencies worldwide including the UK's National Institute for Health and Clinical Excellence (NICE), Scotland's Scottish Medicines Consortium (SMC), Canada's Canadian Agency for Drugs and Technologies (CADTH) in Health Common Drug Review and Pan‑Canadian Oncology Drug Review, Australia's Pharmaceutical Benefits Advisory Committee (PBAC), France's Haute Autorité de Santé (HAS), and Germany's The Federal Joint Committee (G-BA), as when they used observational studies in HTA decisions. A total of 1,840 HTA decisions were examined, excluding reviews that did not include decisions, clinical data, or instances where it was unclear if observational data was used. Decisions were classified as 'positive' or 'negative'. From this large sample, only 106 decisions/HTA evaluations (6%) incorporated observational data while the remaining 1,734 did not (Liden et al., 2015). Of those HTA evaluations that included and considered observational data, 77% resulted in positive decisions Of the HTA evaluations that did not consider observational data, only 67% resulted in a positive decision ($p=0.025$).

The findings of this study suggest that HTA bodies have not yet taken full advantage of the benefits of RWE in the general assessment of innovative technologies, as much as regulators have, but have limited its use to pricing negotiations. Yet, the trend towards more integrated assessments between HTA and regulatory bodies may create the appropriate conditions to appreciate and further use RWE (EMA, 2017, NICE, 2016).

3.2.2 Conditional reimbursement and additional evidence generation decisions

Payers, physicians and sometimes patients must balance uncertainties about the net benefits with uncertainties of both financial costs and forgone opportunities offered by alternative treatments. As we have discussed in previous sections, legislators and drug regulatory agencies have responded to the challenge by introducing flexible licensing pathways. These include accelerated approval (in the US) and conditional marketing authorization/approval (in the EU and Japan) as well as other regulatory tools for situations where “the benefits to public health of [immediate availability] outweigh the risks inherent in the fact that additional data are still required” (European Union, 2006). Payers have responded with managed entry agreements (MEAs), coverage with evidence development (CED), and similar flexible approaches to develop much-needed information on real-world effectiveness and value (Baird et al., 2014).

Meeting marketplace demands for proving the value of new products requires more data than the industry has routinely produced. These data include evidence from comparative effectiveness research (CER), including RCTs, pragmatic trials, observational studies and meta-analyses. The CER is being used by payers for most types of post-approval decisions.

Table 7 below evaluates nine examples of conditional reimbursement of pharmaceutical products and medical devices. Differing reimbursement conditions are reported in the various country contexts ranging from the UK to the US and Sweden, all demonstrating different approaches to the same of objective of balancing the risks of delayed approval and patient safety. **Error! Reference source not found.**, reports the country context, definition f each reimbursement condition, and the advantages and disadvantages that should be considered for each system.

Table 7: Summary table of conditional reimbursement types

Conditional reimbursement types	Where effective (HTA agency) and source	Definition	Advantages	Disadvantages
Only in research	UK (NICE) [(Claxton et al., 2012) NICE's summary of decisions (NICE, 2017)]	✓ Drug or treatment is recommended for use only in the context of a research study (for e.g. a clinical trial) (Claxton et al., 2012, Chalkidou et al., 2012). ✓ Including medicines, medical devices, diagnostic techniques, surgical procedures and health promotion activities ✓ Not yet enough robust clinical evidence for use in NHS and to inform future NICE guidances – further research should be carried out	✓ Further clinical research or plans for research is deemed to be realistic and costs are deemed to be favourable ✓ Allows NICE an opportunity to take full advantage of RWE and reducing uncertainty by obtaining more evidence ✓ Conducts RWE assessments on public health interventions	✓ Drug or treatment cannot be routinely used ✓ Potentially a costly and lengthy process and NICE has no dedicated budget for research funding to accompany its recommendations to the NHS. ✓ Individuals can only receive this treatment if included in a study ✓ No systematic collaboration between partners and not a systematic process
Only with research	France (HAS/UNCAM) and Sweden (TLV) [(Li et al., 2014), (Walker et al., 2012)]	✓ The drug or treatment is reimbursed by HTAs based on the condition that further research should be done.	✓ Drug or treatment can be routinely used, allowing patients early access to pioneering technologies ✓ Coverage not limited to study participants ✓ Manufacturers have longer to make returns before patent expiration ✓ Regulatory framework	✓ Sweden's TLV process is used exclusively for innovative drugs, has difficulties in interpreting observational studies and with effectiveness studies ✓ France's HAS/UNCAM processes are for medical and surgical procedures only, lacks global funding, collaboration between partners and has no operational system
Conditionally funded field evaluation (CFFE)	Ontario, Canada (Ministry of Health and Long-Term care (MOHLTC)) (Goeree et al., 2010)	✓ Scheme based on concerns that HTA submissions have been too reliant on assumptions about costs and patient preferences, captured across different jurisdictions ✓ Need for quality controls prior to unrestricted diffusion ✓ Treatment or drug may have disruptive effects ✓ Large potential investment ✓ CFFEs studies the safety, efficacy, effectiveness, or cost-effectiveness of a drug or treatment using a pragmatic RCT or observational study ✓ CFFE studies are recommended if a HTA submission is judged to include insufficient information for an evidence-based decision	✓ CFFE study designs are individual; they vary as necessary and range in duration from 1-4 years ✓ CFFEs and RWE has gained recognition from medical community ✓ Conducts RWE assessments on public health interventions	✓ Funding of evidence-based platforms and CFFEs are limited ✓ CFFEs may take many years, and this timing can cause tension between researchers and the political needs in government ✓ CFFEs are resource heavy, and require input throughout the process, for e.g. from opinion leaders, due diligence systems and training of health care staff ✓ System is limited to Ontario region only
Monitored use	Spain (Ministry of Health) (Carbonneil et al., 2009)	✓ A cooperation between HTA organisations, healthcare professionals, and researchers to use data for policy recommendations ✓ Monitored use recommended when there is uncertainty about effectiveness and safety at initial coverage decision stage	✓ The collaboration has dedicated funding ✓ Regulatory framework ✓ Methodological guidance ✓ Operational system	✓ There are no selection criteria for which technologies should be monitored, suggesting allocation of resources is not systematic (Carbonneil et al., 2009).

Interim funding	Australia / Ministry of Health and aging (Carbonneil et al., 2009)	✓ Conducts RWE research on technologies that are (i) safe and effective, but with uncertain cost-effective, or (ii) cost-effective, with uncertain safety and effectiveness	✓ Has dedicated funding ✓ Regulatory framework ✓ Methodological guidance ✓ Operational system	✓ Only medical devices and procedures ✓ No systematic collaboration between partners ✓ Funding not fully adapted ✓ Trial duration is >3 years for conditional coverage ✓ National target population is small, interim funding while awaiting results of international studies
Independent research on medicines	Italy (regional institutions) (Carbonneil et al., 2009)	✓ Provides temporary access to medicines that are not yet available approved by the national agency and still under development ✓ Used for research on rare diseases or high impact diseases in terms of public health or the economy ✓ Used if long-term safety of chronic disease patients is at stake	✓ Conducts RWE assessments on public health interventions ✓ Data collection is funded by the Italian Medicine Agency (AIFA)	✓ For medicines only ✓ No systematic collaboration ✓ No conditional or temporary coverage
Coverage with evidence development / managed entry agreements (MEAs)	Germany (GBA) (Kähm et al., 2016)	✓ MEAs are used for the early integration of innovative treatments ✓ Coverage with evidence development can be granted for non-pharmaceutical interventions, when studied in a clinical setting ✓ The manufacturer is obliged to contribute financially if mainly involving a medical product ✓ Pharmaceutical treatments that have not been approved cannot be covered by “coverage with development plans” ✓ For approved drugs, coverage with development agreements can be concluded between specific payers (health insurances) and pharmaceutical companies to determine the level of refund conditional on measurable therapeutic success	✓ A growing area in German health economic literature ✓ Allows for the early introduction of approved innovative treatments on the basis that health insurance must fulfil their “care taking” obligation	✓ Due to the confidential nature of many MEAs, a systematic review of published sources provides an incomplete picture of the use of MEAs in Germany. ✓ MEAs lack a mechanism to measure the success of a therapy due to the following issues: a lack of defined parameters, individual patient factors are not considered, and criteria for qualitative data collection and study designs is lacking. ✓ Risk sharing requires data reviewing and monitoring, leading to a high administrative burden for hospitals and insurance funds ✓ Further economic, legal and ethical research is necessary to exploit potential for MEAs in the German statutory health insurance
Coverage with evidence development	US (CMS) (Carbonneil et al., 2009)	✓ Coverage policies developed by Medicare aiming at reducing uncertainty with RWE ✓ Required where existing medical evidence is insufficient for effectiveness, safety or cost-effectiveness. ✓ Two types of coverage are contingent on additional evidence: (i) with study participation (restricted to patients receiving intervention as part of a clinical trial or registry), and (ii) with appropriateness determination (additional clinical information to determine appropriateness of coverage).	✓ Publicly funded through CMS for clinical costs, and stakeholders for other costs ✓ Has a partial methodological framework	✓ No dedicated global funding ✓ No systematic collaboration between partners ✓ Not a systematic process

On the operational level, the paradigm shift is becoming apparent by the growing number of managed entry agreements (MEAs) concluded in some healthcare environments. Although uptake of these and other arrangements has not been uniformed across payers, especially in the US. MEAs are voluntary formal arrangements between payers and manufacturers with the aim of sharing the financial risk due to uncertainty around the clinical and cost-effectiveness of innovative technologies at the time of introduction (Eichler et al., 2015).

MEAs can take different forms, including performance-based agreements, coverage with evidence development (CED), and disease management programs (Ferrario and Kanavos, 2013).

The flexibility of MEAs in addressing post-initial licensing uncertainty and enabling access to expensive treatments provides an opportunity for synergies with regulatory initiatives. Under an AL paradigm it is anticipated that a growing number of post-authorization safety and/or efficacy studies will be imposed by regulators. There is no compelling reason why these studies could not be prospectively planned and aligned with post-licensing evidence generation foreseen by payers under an MEA/CED scheme (Eichler et al., 2015).

A recent analysis of coverage decisions in the EU showed that a sizable fraction of compounds approved under conditional marketing authorization (CMA) was subsequently reimbursed with a MEA. (CMA is an EU regulatory pathway similar to “Accelerated Approval” in the US and, in spirit, close to the AL concept, although narrower in scope.) The MEAs put in place comprised initial restriction of reimbursement for small high unmet-need subpopulations, performance, or financial risk sharing and ongoing evidence development plans (Spearpoint et al., 2014).

Following a drug from pre-market through the HTA assessment and up to post-marketing studies allows more time to collect evidence which will feed into the HTA. It also enables an early assessment of the possible budget impact and to verify forecasts with post-marketing data. Finally, information from post-launch studies can be used to update national recommendations on the use of the drug. If linked with adaptive licensing this can become a powerful instrument to manage the introduction of new medicines to minimise the impact on the healthcare system (Ferrario and Kanavos, 2013).

The biopharmaceutical industry is faced with a complex set of challenges to generate evidence for post-approval decisions by health care system stakeholders. Uncertainty remains as to how the industry and payers use post-approval studies to guide decision-making on pricing and reimbursement status. Correspondingly, there is uncertainty on whether the industry's investment in CER will have a positive return on investment in terms of reimbursement and market access (Milne et al., 2015).

3.2.3 Supporting Performance-Based Risk-Sharing Agreements and other innovative models of pricing and reimbursement

There is a significant and growing interest among both payers and producers of medical products for agreements that involve a “pay-for-performance” or “risk-sharing” elements. These payment schemes—called “performance-based risk-sharing arrangements” (PBRSAs)—involve a plan by which the performance of the product is tracked in a defined patient population over a specified period and the amount or level of reimbursement is based on the health and cost outcomes achieved. (Adamski et al., 2010, Garrison et al., 2013). These schemes go under different names in different jurisdictions, but sometimes overlap with the provisions for conditional reimbursement (e.g. ‘‘risk-sharing’’, ‘‘coverage with evidence development’’, ‘‘only with research’’, ‘‘field evaluations’’). Both have the common feature that the technology concerned is granted reimbursement if more data are collected. A final price and/or reimbursement status for the technology determined based on the results of the data collection exercise (Drummond, 2015).

There has always been considerable uncertainty at product launch about the ultimate real-world clinical and economic performance of new medical products. There is increasing payer uncertainty and concomitant of financial risk when reimbursing a potentially ineffective new treatment in a real-world scenario. The rising price of the new treatments, whether a biologic, device, or other medical technology adds to this risk. If payers are reluctant to recommend treatments, manufacturers face the risk of reduced revenue for a product they regard as delivering value. PBRSAs represent one mechanism for reducing uncertainty through greater investment in evidence collection while a technology is in use within a health care system (Garrison et al., 2013).

Perceived benefits of PBRSAs:

- Potential to enhance coverage decisions and strengthen existing evidence based on the benefits and costs of innovative technologies
- Enable payers to participate in the research process
- Allow hospitals and clinicians to monitor procedures being performed more closely and manage costs until benefit is substantiated
- Encourage industry to generate the data needed to support the value claims of their innovations
- Allow earlier access for patients to potentially valuable treatments than they might otherwise be granted.

A useful example of PBRSAs is the reimbursement of Velcade (bortezomib) for multiple myeloma in the UK. During a NICE technology appraisal, an ‘outcome guarantee’ scheme was suggested by the manufacturer. The NHS agreed to ensure that ‘all suitable patients’

would have access to the drug. In return, the manufacturer agreed to refund treatment costs for patients who failed to respond (based on M-protein) (NICE, 2007).

3.3 For the clinicians and other healthcare practitioners

Medical and health care is one of the most dynamic human disciplines, with constantly evolving new research. Clinicians, healthcare practitioners (HCPs) and professional association are encouraged to consider new clinical data (RCTs and observational), furthermore they should consider economic and other patient outcomes aspects.

3.3.1 In the development of locally relevant clinical guidelines

Clinicians and HCPs are heavily involved in the development of locally relevant Clinical Practice Guidelines. RWE helps to overcome the transferability issues with evidence generated within a country for the local population and abroad. A recent review identified 43 different CPRD (Clinical Practice Research Datalink; longitudinal database containing anonymised EHR data) studies across 12 disease areas that had been used in the development of NICE clinical practice guidelines. This shows a slow uptake of RWE in clinical and therapeutic guidelines (as provided by UK governmental structures). Thus, there seems to be an increasing trend in the use of healthcare system data to inform clinical practice, especially as the real world validity of clinical trials is being questioned (Oyinlola et al., 2016).

3.3.2 Identifying subpopulations

RWE aims to conduct observational studies for the targeted claim in subpopulations. To facilitate this, a structured observational study design is needed with the ability to follow a patient cohort and allow for sub-set analysis (Gill et al., 2016). In the pre-approval setting RWE can enhance the effectiveness of RCTs via the identification of patients from specific subpopulations (i.e. background epidemiology) which could potentially lead to shorter and more effective trial periods (Bonnelye et al., 2015). In the post-approval setting, RWE analyses can highlight subgroups that would benefit (or be harmed) most.

A pragmatic trial including patients receiving Drug Eluting Stents (DES) was established for a ‘field evaluation’. Coverage was provided for the stents in the trial. Analysis of the produced registry data found that DES was more effective only in patients at high risk of stenosis (those with diabetes, or particularly long or narrow lesions). This represented about 30% of the whole patient population. This is a prime example of RWE use that led to between $35-58 million in savings, compared with the potential uncontrolled adoption of DES (Goeree et al., 2010).

3.3.3 Professional associations in value assessment of alternative interventions

Professional associations have been developing a series of tools that serve as a basis for value assessment frameworks such as The American Society of Clinical Oncology (ASCO) Value Assessment Framework For Cancer Treatments (Schnipper et al., 2015, Schnipper et al., 2016), the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) (Cherny et al., 2015), the American College of Cardiology and the American Heart Association (ACC-AHA) Statement on Cost/Value Methodology in Clinical Practice Guidelines and Performance Measures (Anderson et al., 2014), the National Comprehensive Cancer Network (NCCN) Evidence Blocks (National Comprehensive Cancer Network, 2015), the Institute for Clinical and Economic Review (ICER) Value Assessment Framework (ICER, 2017), or the Society of Memorial Sloan Kettering Drug Abacus (MSKCC, 2017). Their role is to go beyond traditional risk-benefit analyses to incorporate other dimensions, such as costs, quality of life, affordability and innovation. In all dimensions, RWE's role in collecting continuous information on treatment alternatives is key.

3.4 For patients

Patient groups are getting more involved and are putting more pressure into HTA decision-making. They want to participate and be part of the decision-making process. Broader and more systematic involvement in decision-making of patients and their advocates also offers an opportunity to enlist patient support for the secondary use of health data (or the setting up of registries) to enable evidence generation through the post-licensing phase (Eichler et al., 2015).

Early product entry in niche indications will likely use registries to collect effectiveness, safety and HTA information. RWE has a potential to support safe and timely access to medicines for patients. Patients experience can be captured through specific instruments in real settings and to incorporate treatment benefits that are relevant to the patients.

Early access to safe treatments is one of the key requirements from patients. However, some patients are willing to trade off an uncertain safety and effectiveness status in order to access treatments earlier. Patients and their advocates emphasize that drug development and market access should not only benefit patients in some distant future state, but should also address the unmet needs of the current generation of patients (Eichler et al., 2015). Patients groups that have the most unmet needs are patients with chronic, slow, irreversibly progressing or rare diseases. For these unsatisfactory treatment options, patients make the same plea for urgent access as do those with fast progressing conditions.

By involving Patient Associations from early on and through the adoption of treatments into the standard of care, the quality of new and emerging technologies can be better communicated to users. Approaches in the US (accelerated approval) and the EU (conditional marketing authority), for example, allow patients to be informed and involved

with early and interactive decision-making processes. In turn, patients can contribute to setting thresholds of risk tolerance and acceptable levels of uncertainty. However, these approaches must be mindful of the differences in tolerance amongst socioeconomic groups, and the impact that socio-political factors or experience of adverse events may have (Eichler et al., 2015).

Patient experiences are captured through specific instruments in real settings and to incorporate relevant treatment benefits. Patient reported outcome measures (PROMs) provide additional "patient-centred" data which is unique in capturing the patient's own opinion on the impact of their disease or disorder, and its treatment, on their life. Patients' experiences are captured through disease-specific instruments in real-world settings to incorporate PROs. (Galson and Simon, 2016).

3.5 For the pharmaceutical industry

The ability to quickly transform RWE sources such as claims data or electronic medical records into evidence can improve health outcomes for patients by helping pharmaceutical firms be more efficient in drug development and smarter in commercialisation.

Industry views RWE as an additional opportunity to demonstrate the value of medicines, for both the patient and the health system. It may also provide new opportunities for industry to work with payers to advance novel approaches to pricing and reimbursement (Nason, 2014).

Pharmaceutical industry enables RWE in multiple ways.

- RWE helps design efficient trials: epidemiological trends, treatment patterns, patient adherence and disease management opportunities.
- Develop products and therapies: Assess uses of current competitive in-market products, design inclusion/exclusion criteria for clinical trials, perform predictive models on virtual trials, identify patients for recruitment, and identify unintended uses/indications (i.e., Phase IV leads).
- Assess products and therapies in use: Observe drug safety, compare product effectiveness, assess health economics, and design pay-for-performance criteria.
- Target products and services: Identify underserved patient populations, identify high-cost areas for risk-based product pricing, identify subpopulations with superior product response, and track message effectiveness through prescribing behaviour (Cattell et al., 2011).

Pharmaceutical industry analyses of past industry performance suggest that development programs targeting smaller, better-defined populations have higher overall success rates than those aiming at larger, heterogeneous populations.

The most common marketing strategy used by the pharmaceutical industry is the "blockbuster" approach; this involves obtaining licenses and broad population coverage. This phase is followed by detecting and generating evidence of specific effects in patient sub-groups. This search for the differentiation of effects is often triggered by incoming competitor products. The "small to big" business model aims to initially focus on a targeted population to get an earlier licensing. Then to progressively extend the indications to additional sub-populations. Consequently, the total eligible treatment population grows in sequential steps (Eichler et al., 2015).

Additionally, the industry appeals to RWE to improve investment decisions and optimize portfolio.

Case study: Use of databases in the USA – a pharmaceutical perspective

In response to rising costs, major changes occurred in the US Health Care System during the past decades. In the late 1980s, providers and life science companies were interested in the cost effectiveness of different therapies in Real World Clinical and Evidence Based Medicine.

The Clinton administration's proposed Health Security Act (HSA, 1993 (US Congress, 1993)) drew attention to information systems and data collection strategies. It called for the establishment of a National Health Board to oversee the creation of an electronic data network consisting of regional centres that collect, compile, and transmit information. The board, among other duties, provided technical assistance on the promotion of community-based health information systems and the promotion of patient care information systems that collect data at the point of care or as a by-product of the delivery of care.

The HSA further specified the use of uniform paper forms containing standard data elements, definitions, and instructions for completion; requirements for use of uniform health data sets with common definitions to standardize the collection and transmission of data in electronic form; uniform presentation requirements for data in electronic form; and electronic data interchange requirements for the exchange of data among automated health information systems.

In 2009, the open government directive as well as the consequent actions of the Department of Health and Human Services (HHS) under the Health Data Initiative started to share data from agencies like the centres for Medicare and Medicaid Services, the Food and Drug Administration (FDA) and the Center for Disease Control. The Health Information Technology for Economic and Clinical Health (HITECH) Act (2009) (Congress, 2009) authorized incentive payments for providers to use EMRs, with the objective driving quick adoption of this tool in order to align the method to collect information. In March 2010, the Affordable Care Act, included a provision that authorized the HHS to release data that promote transparency in the markets for healthcare and health insurance. To comply with the Health Insurance Portability and Accountability Act (HIPAA) patient confidentiality standard, patients' names and personal information must be removed from the records filed into large database to de identify datasets.

The pharmaceutical industry, providers and payers have an unmet need for big data analyses to understand issues associated to variability in health care quality and services as well as to address the rapid escalating health care costs and spending.

Many health Database Organizations were created to collect this data from the Public/Governmental and private/HMOs institutions.

Currently, claims, hospital discharge and Electronic Medical Charts databases are being used by the Pharma Company's Health Economics and Outcomes Research teams with the following objectives:

- Assess trends in health care costs, utilization and outcomes for diseases
- Analyse diseases/ conditions prevalent among populations
- Determine the cost of burden of a disease.
- Assess direct and indirect costs linked to a clinical condition
- Understand how a drug is performing in the day to day clinical practice without the controlled/strict environment of RCTs.
- Populate health Economic Models as well as Innovative Pricing Models (financial, outcome based, services, etc.).

An example of how these databases can be used:

- Real-World Treatment Patterns of Everolimus for Advanced Breast Cancer: A Multi-Country Chart Review Study (Hamm et al., 2015)
- Comparison of medical costs and healthcare resource utilization of post-menopausal women with HR+/HER2- metastatic breast cancer receiving Everolimus-based therapy or chemotherapy: a retrospective claims database analysis (Li et al., 2016).

3.5.1 Modelling cost-effectiveness

A challenge for decision-makers is the potential gap between the estimated cost-effectiveness of a treatment at the time a funding decision is made and real-world cost-effectiveness. This challenge, arising due to limited data availability to model cost-effectiveness prior to widespread use, has been intensified by growing expectations of early access to promising new treatments. This has led to increasing interest in coverage with evidence development (CED) recommendations, where interim funding is provided while additional evidence is collected. Thus, RWE can inform development for example providing information on existing therapies and on the profile of patients needing treatment (Parkinson et al., 2016).

3.5.2 Optimizing return on investment

The pharmaceutical industry uses RWE when allocating resources to the research and development of new treatments. To optimize return on investment, companies use clinical evidence to inform pipeline strategies. By isolating the most promising compounds early in the R&D process, pharmaceutical companies can use RWE to allocate resources to those that meet patient demand, and so enhance risk management. Pharmaceutical companies may also be able to identify new opportunities for treatment indications and extensions by analysing drug utilization databases. Finally, RWE enables the pharmaceutical industry to monitor the safety and efficacy of marketed treatments, ensuring the anticipated patient benefit is maintained in the real-world environment. This in turn improves the supply of effective and safe treatments to healthcare providers and patients, and improves the adherence to treatments.

3.6 For the healthcare system as a whole

RWE is increasingly considered a viable data source now that the capabilities of healthcare systems allow information to be captured as part of routine monitoring. As the ability to capture this data becomes easier, payers and decision-makers are more interested in use of RWE with a wider scope. Furthermore, methods employed to establish value-based healthcare benefit design will demand more RWE. Identifying the more efficient disease management pathways will help to alleviate the resource constraint to healthcare systems worldwide.

RWE also can be used to monitor health care system performance. The UK government plans to establish a ‘7 days a week NHS’ following the Freemantle et al. report that used RWE to check the hypothesis that there are more in-hospital deaths amongst weekend-admission patients compared to those admitted mid-week. The authors used the ‘Hospital Episode Statistics’ database, which contains information on every hospital admission in the NHS. It was found that patients admitted on a Saturday or Sunday face an increased likelihood of death within 30 days, even when severity of illness is considered (through statistical modelling). Although there are confounding factors at play and unknown proportions of unavoidable deaths (Department of Health (UK), 2015), the authors argue that the inferior outcomes are because of the reduced level of the support services in NHS hospitals at the weekend (Freemantle et al., 2015). This example illustrates that RWE can provide additional insight on the healthcare system effectiveness and certain evidence based actions can be taken to make a positive change.

Another aspect of the opportunities provided by RWE for the health care system is influence on the development of clinical practice guidelines and the assessment of whether practitioners are following them. Payers use evidence-based guidelines to promote effective health diagnoses and treatments for their members and to ensure that members are not

subject to harmful or wasteful care. Payer guidelines inform coverage, but the content of these guidelines relies on the same evidence base as clinical treatment guidelines.

Standardised evidence also helps address issues such as inappropriate variability among healthcare professionals in the provision of care (Farquhar et al., 2003). Examples of this are clinical practice guidelines. In the UK, they are developed by the NICE. These guidelines are based on clinical and cost-effectiveness evidence. One of the reliable RWE sources is patient records databases. The Clinical Practice Research Datalink (CPRD) is a government-funded database of anonymised primary care records (over 11.3 million patients). A recent review identified 43 different CPRD studies across 12 disease areas that were used in the development of NICE clinical practice guidelines (Oyinlola et al., 2016). The same database could be used to assess whether family physicians are adhering to NICE guidelines.

RWE and qualitative data

Another area of research that might be prominent in the future is the use of qualitative methods, in particular for implementation research. Either impact of interventions on organizational routines, behaviours or overall cultures are some of the factors that might be determinant of success. Although most of this research is specifically undertaken and no regular registries are used, qualitative data can be part of the routine data we use in the future to produce RWE. For instance, qualitative assessments of end of life care complemented clinical RWE in the drafting of the UK's "Care for the Dying Adult" clinical guidelines. The UK's National Clinical Guideline Centre draft for consultation report is heavily informed by qualitative studies that, for example, capture both healthcare professionals and dying people's experiences of prescribing treatment and uncertainties over signs that someone is reaching their final days of life (Department of Health (UK), 2015).

4.0 Challenges and hurdles

4.1 Common methodological challenges

Real-world research is an area of methodological innovation. Compared to clinical trial data, RWE data more closely describes how the product will perform in a broader, more representative population over a longer timeframe, and provides information on comparators and outcomes that are not part of the clinical trial protocol (Fimińska, 2015). There is a wide range of study types and complexities for a typical RWE research program. In this section, we present a commentary about the two common methodological issues to deal with in RWE research; confounding and information bias (focusing on misclassification), as well as some other potential sources of error in the use of RWE. For a more detailed account of the principles of observational data analysis and critical interpretation of results, we recommend the reading of epidemiology and biostatistics manuals such as those written by Rothman, Greenland, Lash, Fox and Fink (Rothman, 2012, Rothman et al., 2008, Lash et al., 2009), as well as specific scientific papers suggested in each of the topics in this section.

4.1.1 Confounding

RWE research is typically observational, either based on registries or administrative datasets. The main methodological concern is confounding due to the lack of randomization. In non-randomized studies, patients are assigned to a treatment group as a result of physician choice, creating a risk that patient characteristics in treatment groups are systematically different. For example, physicians may demonstrate channelling bias by assigning high-risk patients to the therapy considered more effective (Lobo et al., 2006).

Therefore, these potential biases need to be addressed in both the study design and analysis phases. Bias can be prevented in the study design by including a large sample size with a diversity of care settings and through specification (restricting the population to those with a specific level of the confounder variable) or matching (case-control or nested case-control studies)(Jepsen et al., 2004). The approaches used to reduce bias in analysis phase include stratification, matching (achieving a balance in observed characteristics between the patient groups such as propensity scores) and multivariate regression (adjusting estimated treatment effects using patients' clinical and other characteristics at study onset). For example, Béland et al (Beland et al., 2011) undertook a retrospective cohort study to compare treatment persistence, cost and incremental cost/persistence ratios across individual new antidepressants, using a public prescription database in Quebec (Canada). To correct for potential selection bias and confounding, they performed a regression analysis in which the dependent variables were treatment non-persistence, health care costs and cost-persistence ratio. The independent (explanatory) variables were antidepressant at treatment initiation, physician speciality, patient's age, gender and socioeconomic status, antidepressant dose, history of antidepressant treatment and overall health status.

The main problems here lie in having enough data on possible confounders to make the adjustments, through either multivariable regression or propensity scoring, and in needing an approach to deal with unknown confounders. The main limitation of propensity score is that is based on observable characteristics. Therefore, it does not resolve the problem of unobserved heterogeneity.

The approach favoured in many economic analyses is to use an instrumental variable (IV) in the regression analysis. An IV is correlated with patients' treatment allocation based on other covariates. For example, in an evaluation of diabetes treatment, Prentice et al (Prentice et al., 2014) used variation in physician prescribing (i.e. frequency of use of one drug vs. another) as an IV, since these prescribing variations would influence treatment while being effectively random with respect to outcome. However, quite often IV does not resolve the problem. The main challenge is to find the adequate instrument, which often has not been registered. Future research should consider variables that might be used as instruments, especially when is well known that some confounders will never be measured or registered.

4.1.2 Information bias and misclassification

Information bias in general can be differential (when the misclassification depends on the exposure or other variables) or non-differential (when the misclassification is random, for example, due data entry errors)(Jepsen et al., 2004). According to an ISPOR task force report on approaches to mitigate bias and confounding in observational studies, there are two major types of differential classification bias (Cox et al., 2009)

- Misclassification of exposure. Measurement errors sue to the manner or time of classification. For example, self-reported exposure to events in the distant past that cause recall bias potentially under-represent exposure and impact results. Another typical example is when patients receive a treatment from their pharmacist but might not adhere to it, which might lead to underestimation of the treatment effect as patients do not receive the correct dose (unlike in RCTs). There is very limited research regarding studies that have measured the impact of the bias on the assessment of the effect of medication adherence on health outcomes (Di Martino et al., 2015).
- Misclassification of outcomes. Another type of misclassification is based on the outcomes. This may occur, for instance, when the observation period is not long enough so outcomes can be recorded as an adverse event rather than an event related to a pre-existing comorbidity.

4.1.3 Missing data, heterogeneity and other sources of potential errors

Any research runs the risk of having of missing data, which influences study data quality, results and conclusions. Ignoring missing data may cause bias of unknown size. Problems

may include missing data and its retrospective interpretation or potential remedy at the data collection stage, accuracy, lack of adverse event data, and unintended bias. This contrasts with clinical trials in which extensive measures are taken to reduce variability, to ensure the quality of the data collected, and to obtain detailed data on every adverse event that occurs. Data quality control is essential for providing confidence in the reliability of RWE sources.

The data could be missing due to a variety of reasons: variation in disease coding (or failure to code) and differences in missing data across patients and time, broken data linkage as well as data not being captured at all, and they require effortful consideration on the part of researchers. There are multiple methods that help to deal with this issue: simple mean imputation, regression mean imputation, last observation carried out, multiple imputation, mixed models etc. Any of these methods have their pros and cons and should be considered carefully.

Another methodological challenge is revealing variations across individuals. This heterogeneity, which has been defined as “the proportion of the variability that can be defined by a set of observed (known) characteristics at the time of the analysis” (Espinoza et al., 2014) is usually explored through subgroup analysis. However, more recently has been suggested that ex-post choices or treatment selection can be a good predictor of individual treatment effects (Basu, 2011). This is an area that needs further research, where RWE may have a significant role.

Furthermore, there are a number of additional sources of error that may arise in the use of RWE to ascertain associations that will not be covered in depth in this paper such as selection bias, lead-time bias the ecological fallacy, or the Simpson’s paradox (Hammer et al., 2009).

4.2 Generic Challenges in Using Real World Evidence

As the use of RWE increases, confidentiality issues become increasingly challenging. Many data generators (providers, payers, and registries) today insist that their data remain locally stored, citing data security and patient privacy concerns; only aggregate-level results may leave their systems after local analysis of individual-level data (Mandl and Kohane, 2015). Linkage of additional data sources to enrich clinical information faces fewer privacy hurdles when conducted locally by the data generators. This leads logically to a network of multiple analytic nodes, each of which may be the result of local linkage activities itself. The US Sentinel System, Exploring and Understanding Adverse Drug Reactions, and European Medical Informatics Framework follow this principle (Laheij et al., 2004, Schneeweiss et al., 2016, Platt et al., 2012).

The data remain at the site of the data generators, including all local security and privacy precautions, and mostly aggregated results will be shared in the network (Curtis et al.,

2012). New privacy regulations, for instance, in Europe, directive 2016/680, may make the organization of such networks more complicated.

In addition, much RWE is collected for purposes other than research. For example, information on physician prescribing might be collected to monitor physician practice. Administrative claims data might be collected to reimburse health care providers or hospitals. Therefore, those managing the data may not see their role in making data available for research or are not resourced enough to offer this service. Also, in some settings there may be ethical or legal restrictions on the use of data for purpose other than those for which they were originally collected. Consequently, institutional arrangements for allowing the access to data vary and usage is often limited

Finally, many existing datasets do not include diagnostic information; this limits the usefulness of the data for monitoring health care utilization and for making treatment comparisons. For example, it may be easy to obtain data on the number of units of a given drug that are prescribed, but without diagnostic information it is not possible to assess whether the drug has been appropriately prescribed. Therefore, in some cases it may be necessary to undertake a prospective study, whereby the analyst can control what data are collected (Gliklich et al., 2014).

4.3 Methodological resources for the researchers

While there is growing demand for information about comparative effectiveness, there is substantial debate about whether and when observational studies have sufficient quality to support decision-making. Several tests were developed to check the quality of those studies:

- An 11-item checklist about data and methods (the GRACE checklist) was developed through literature review and consultation with experts from professional societies, payer groups, the private sector, and academia. This checklist provides guidance to help determine which observational studies of comparative effectiveness have used strong scientific methods and good data that are fit for purpose and merit consideration for decision-making. The checklist contains a parsimonious set of elements that can be objectively assessed in published studies, and user testing shows that it can be successfully applied to studies of drugs, medical devices, and clinical and surgical interventions (Dreyer et al., 2014).
- Four ISPOR Good Practices Task Forces developed consensus-based questionnaires to help decision-makers evaluate 1) prospective and 2) retrospective observational studies, 3) network meta-analysis (indirect treatment comparison), and 4) decision analytic modelling studies with greater uniformity and transparency. Separately developed questionnaires were combined into a single questionnaire consisting of 33 items. These were divided into two domains: relevance and credibility. Relevance addresses the extent to which findings, if accurate, apply to the

setting of interest to the decision-maker. Credibility addresses the extent to which the study findings accurately answer the study question. The questionnaire provides a guide for assessing the degree of confidence that should be placed from observational studies and promotes awareness of the subtleties involved in evaluating those (Berger et al., 2014).

- The Patient-Centered Outcomes Research Institute (PCORI) methodology is a standard for studies of diagnostic tests recommends that investigators consult and use broadly accepted checklists for reporting study results and assessing study quality (Leeflang et al., 2007). PCORI specifically encourages investigators to consult and use the following checklists:
  - CONSORT (Consolidated Standards of Reporting Trials)
  - STARD (Standards for the Reporting of Diagnostic Accuracy Studies) checklist
  - QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies 2)
  - The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Initiative developed recommendations on what should be included in an accurate and complete report of an observational study. The STROBE Statement contains 22 items: 18 items are common to all three study designs and four are specific for cohort, case-control, or cross-sectional studies (von Elm et al., 2008).

Besides the methodological suggestions from the academia, the FDA and the National Institutes of Health (NIH) are working on ways to harmonize data collected from EHRs, claims data, and registries, and to facilitate the provision of actual data that does not require external review or interpretation. To its credit, the FDA (and multiple European countries) has embraced the positive uses for RWE, particularly its potential for informing hypotheses and study design, and for increasing our knowledge of the effects of a product on more diverse populations than those studied in clinical trials.

Finally, it is worth mentioning that there are several ways to find available real-world data. One starting point is to look at meta-databases – i.e. databases of databases. The biggest meta-databases are ISPOR Digest of Databases, the French initiative B.R.I.D.G.E. TO DATA, or the ENCePP (European Network of Centres for Pharmacoepidemiology and Pharmacovigilance). Whilst the meta-databases list an impressive number of or real-world data sources, there is a question of completeness and one needs to figure out whether they are fit-for-purpose.

5.0 Case studies in Latin America

Workshops conducted across Latin America provided a starting point for sharing RWE practices, a vital step to growing the appropriate use of RWE in this region. Sharing good practices facilitates what worked well and when. This knowledge can subsequently be fed into the actions discussed earlier (i.e. knowing what is fit for purpose in RWE, linking research and innovation to RWE in the health system, and addressing data privacy issues). The knowledge also helps to build capacity across the countries and amongst stakeholder groups by continually informing people of approaches and methods in place for RWE.

5.1 Argentina

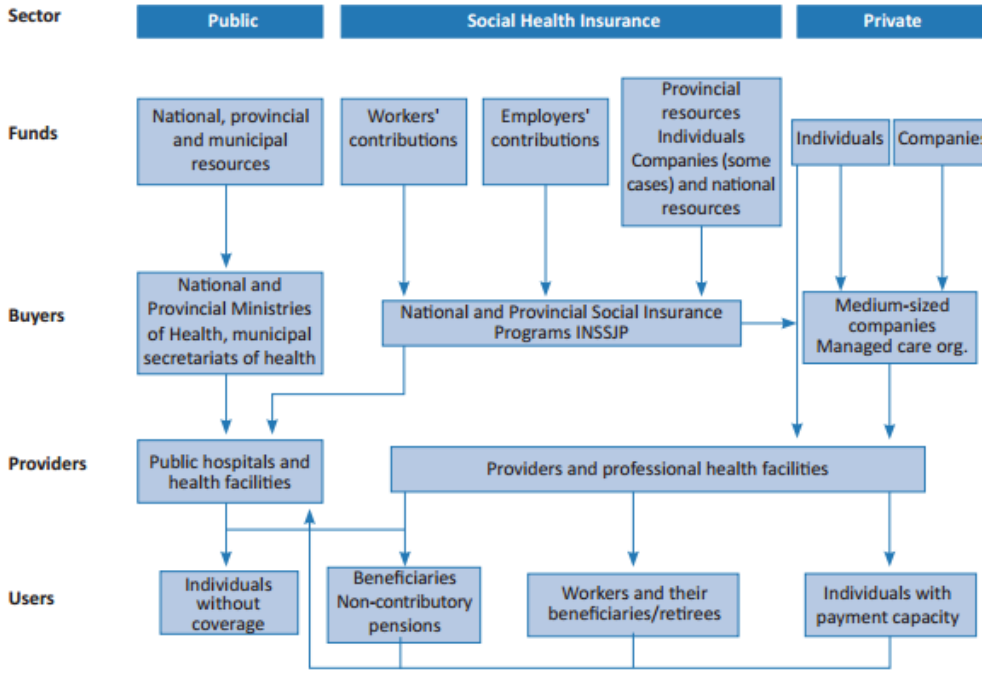
5.1.1 Healthcare system in Argentina

Argentina's health system is grounded on a federal political structure, and is profoundly decentralized in terms of healthcare provision and administration. Healthcare services are jointly funded and managed by three subsectors: public, social security and private. The public subsector covers roughly half of the country's population and provides funds and healthcare services based on 24 decentralized institutions, i.e., provincial Ministries of Health and the National Ministry of Health acts as the coordinating institution (Bello and Becerril-Montekio, 2011). These 24 jurisdictions with intermediate power are responsible for providing public healthcare in their corresponding territories and are thus capable of making decisions related to health policies independently (Giovanella et al., 2012).

In theory, coverage is universal, but the population seeking care in the public sector are mostly those not covered by social security. In general, these are non-registered self-employed workers and unemployed individuals, ultimately an inactive population with no purchasing power (Giovanella et al., 2012). The public sector includes the national and provincial Ministries of Health as well as the network of public hospitals and primary health care units which provide care to the uninsured population. This sector is financed primarily by taxes.

The social security sector, or Obras Sociales (OS), covers all workers within the formal economy and their families. Most OS operate through contracts with private providers and are financed through mandatory payroll contributions from both employers and employees. Finally, the private sector includes all those private providers offering services to individuals and all those with private health insurance. This sector also includes private insurance agencies called Prepaid Medicine Enterprises, financed mostly through premiums paid by families and/or employers (Bello and Becerril-Montekio, 2011).

Figure 2: Schematic view of healthcare system in Argentina



Source: (Bello and Becerril-Montekio, 2011)

5.1.2 Real World Evidence: Overview in Argentina

Although in the last few years the terms “Real World Evidence” has become more popular in Argentina, the Food, Drug and Health Technology National Agency (Administración Nacional de Medicamentos, Alimentos y Tecnología Médica - ANMAT) has not incorporated RWE to any procedures. This means there is still no formal use of this type of data in the regulatory setting. In general, the pharmaceutical industry is the stakeholder that seems more interested in this type of study designs and many workshops and activities have been developed, but they have not had an impact on the regulatory activity yet.

In contrast, RWE is starting to gain the interest of local HTA bodies. Until recently, Argentina did not have an official national HTA agency producing binding recommendations so this type of assessment was only done in specific institutions before acquisitions of costly technologies. Even then, it was used more to evaluate the return of investment rather than a full-fledged formal HTA. However, in May 2017, Ministry of Health issued a new resolution through the bureau that regulates the activity of OS and private healthcare insurances and providers, the Superintendence of Health Services (Superintendencia de Servicios de Salud - SSS). This measure established an obligation to conduct and present a formal HTA when a new health technology is introduced in compulsory benefit packages (Plan Medico Obligatorio - PMO) or in the national formulary (Sistema Único de Reembolso - SUR). This requirement will promote the development of budget impact analyses and economic evaluations. It will potentially foster an increase in assessments based on RWE as the

methods described in the forms (Annex I) and supporting materials (Annex III) suggest that the use of observational study evidence will be accepted. However, it is considered of low quality compared to RCT evidence (Resolución 370-E/2017 including Annex III) (Superintendencia de Servicios de Salud, 2017). The country holds sufficient capabilities to conduct these HTAs given the number of prestigious institutions that have been working on these type of assessments. Following the research published by Lifschitz et al (2017) a number of public and private institutions have developed sufficient local capacity to generalize the use of HTAs in healthcare decision-making (Lifschitz et al., 2017). This may constitute a cornerstone in the dissemination of RWE use. The following are some of the key HTAs in the public sector in Argentina:

- Within ANMAT, there is an HTA Directorate that has developed a series of Abbreviated HTA Reports (Informes Ultrarrápidos de Evaluación de Tecnologías Sanitarias - IURETS) that may consider RWE, yet respecting the traditional evidence hierarchy (Phillips et al., 2009).
- The HTA Coordination Unit of the Ministry of Health (Unidad Coordinadora de Evaluación y Ejecución de Tecnologías en Salud - UCEETS) was created in 2009 with the aim to coordinate public HTA initiatives to generate high quality scientific information on effectiveness, cost and global impact of health technologies. This unit brings together representatives, among others, from the SSS, the ANMAT, the national hospitals, the National Cancer Institute, The National Institute for Social Services for the Retirees (Programa de Atención Médica Integral - PAMI).
- Other official initiatives that helped establish the grounds for capacity building in HTAs are the HTA Area within the National Cancer Institute, the Argentine Public Network for HTAs (Red Argentina Pública de Evaluación de Tecnologías Sanitarias - RedARETS) and the HTA Network for the Americas (Red de Evaluación de Tecnologías en Salud para las Américas - RedETSA). All of these bodies have researchers that are experienced in the generation and analysis of RWE.

Additionally, there are a number of academic institutions with a focus on HTA with varying maturity and experience such as:

- Institute for Clinical Effectiveness and Health Policy (Instituto de Efectividad Clínica y Sanitaria - IECS): An independent academic institution founded in 2002 and affiliated to the University of Buenos Aires, that is devoted to research, education, and international cooperation. With the ETS and Health Economics Departments, IECS has been conducting health-economic evaluations and complete HTAs of numerous interventions based on RWE and trial data. Researchers from IECS, have also addressed issues with transferability to Argentina and Latin America in general using local RWE to adapt international studies to the local setting. IECS is a member of

INAHTA and the HTA Network for the Americas (Red de Evaluación de Tecnologías en Salud para las Américas - RedETSA).

- The University of Buenos Aires created IMSSET in 2013, an institute fully devoted to research with a focus on HTAs, which has developed a series of clinical guidelines (Tecnologías Tuteladas).
- Also in 2013, the University ISALUD created the HTA Center (Centro de Evaluación de Tecnologías Sanitarias - CETSA) that offers even more capabilities for these types of analyses.

Finally, the pharmaceutical industry has funded economic evaluations that can be used to approximate good value for money for the technologies evaluated. However, so far, the use of these data for pricing has been very limited.

Although RWE is still underdeveloped in Argentina, some data resources exist that can be used to perform this kind of studies. In the three subsectors mentioned before, there are examples of databases that can be useful and we describe some of them in more detail in later sections (Bello and Becerril-Montekio, 2011).

5.1.3 Identified challenges

These subsectors face different barriers regarding the use of data. In the social security or private subsector, some of the problems that exist are related with sharing data with other stakeholders due to the fear of transferring information to competitors or being inspected in actions taken during health care provision.

In the public sector, sometimes there is confusion regarding “ownership” of the data, and these governance issues limit the accessibility for third parties.

One of the key issues in the utilization of RWE, common to all the subsectors, is the difficulty of linking different databases to track and follow patients through the different levels of care. For example, relating hospitalizations with ambulatory care or drug prescriptions to one specific person or deriving outcomes from any of those events.

Another common problem to all subsectors is the lack of a harmonized codification in use, since heterogeneous systems and sub-registries still coexist.

5.1.4 Opportunities and future developments

In general, data generated in the private sector or from social security systems are of better quality than in the public sector. This is partially due to financial incentives to report surveillance data which influences the detail and quality An example of this is the Sumar program for child and maternal healthcare coverage (more detail in 5.1.4.1).

Particularly, in the social security subsector there is an initiative to monitor the utilization of selected technologies. The payers need to provide utilization data to be reimbursed for the cost of these selected technologies. This can be a source of RWE, but the formal use of this data is not well developed.

In the recent months, there have been some developments regarding electronic medical records and the harmonization of codification in the public sector which may help in the future to generate real world evidence.

Existing key data assets

Some of the examples of database uses in Argentina are:

5.1.4.1 The SISA project

Argentina's need for high quality, timely and integrated healthcare data collection systems has historically not been met. Argentina's databases have been divided by the social security sector, private healthcare insurance companies, and the public healthcare system, in itself geographically split into 24 provinces, with each managing their own data collection and development procedures. The fragmentation of management is confounded by using unlinked IT systems, and clashing performance monitoring processes. These differing practices limit the availability of data, and the potential for evaluation, planning and management of services on a unified level.

However, the Argentine Integrated System of Health Information Systems (Sistema Integrado de Información Sanitaria Argentino - SISA) aims to integrate the country's healthcare data management. SISA has begun monitoring facilities, staffing and community services, overseen by the MoH and provincial ministries. SISA aims to be the central meeting place of digital health systems in Argentina, to optimize information management, performance evaluation and decision-making. (Ministerio de Salud de la Nacion, 2017). More specifically, SISA objectives are to monitor and evaluate data collection, evidence-based decision-making, and ensure consistent, secure and accessible information. SISA also aims to foster consultations with communities, centralise information to optimise resources, provide guarantees on the quality, trustworthiness and integrity of information, and finally to strengthen the National MoH and provincial MoHs capability for leadership in health system data collection (Ministerio de Salud de la Nacion, 2017). The ultimate objective is to benefit citizen care through using an integrated federal health information system

The Argentine unique ID cards will be used to achieve these objectives. ID cards will act as the link for a single data repository, a standardized platform to store and manage information from all levels and sources. Several general management registries have been set up by SISA so far. They include the federal registries for healthcare facilities, professionals,

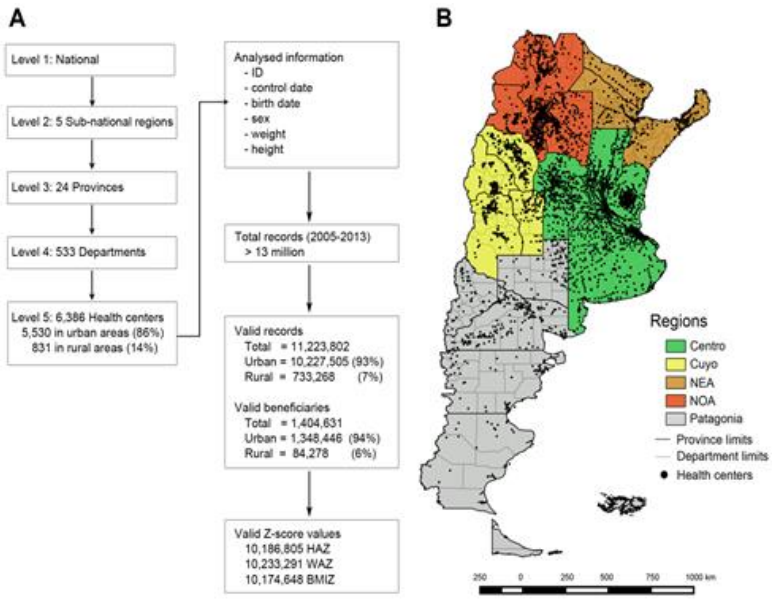
research and an injury surveillance system. SISA has also established access to registers for social information, including data on immunization, blood donations, school health, HIV-AIDS patient management and cardiovascular diseases (Ministerio de Salud de la Nacion, 2017).

The Sumar program

As part of the SISA project, the Sumar program, a pay-for-performance incentives policy was set up in 2012 to complement the child and maternal healthcare already provided by the provinces, Plan Nacer. It was launched to expand coverage to all adolescents and women aged 20-64, and in 2015 it grew to include all men and women aged 64 and under (Center for Global Development, 2016). The Sumar program works by allocating federal funds to the provinces to meet specific health metric goals, and to cover uninsured populations of both children and adults. In some cases, the Sumar program finances the practice registry just to access information and monitor healthcare performance.

The Sumar Program has access to a vast amount of data. For instance, child ambulatory visits were collected, containing data such as weight, height, province, department and health centre. With this data, a study on the trend of undernutrition was conducted for the period 2005-2013 amongst 1.4 million children in 6386 health centres in vulnerable populations. As a result, the prevalence of stunting and underweight decreased 45% (from 21% to 11%) and 38% (from 4% to 2%), respectively. The differences between rural versus urban areas, gender, regions, age, and seasons were identified. Authors of the study concluded that malnutrition prevalence substantially decreased in two programs in Argentina because of universal health coverage (Nunez et al., 2016).

Figure 3: Schematic view of Plan Nacer in Argentina



Source: (Nunez et al., 2016)

5.1.4.2 PAMI – Programa Atención Medica Integral

Argentina has a specific coverage for elderly people similar to Medicare in the United States, called PAMI from its Spanish abbreviation (Programa Atención Medica Integral). This institution has a lot of data on medical assistance of the elderly in Argentina, and in some cases specific registry data of practices for example Implantable Cardiodesfibrilator (ICD). Using this database, a protocol was developed to evaluate the survival rates of the persons enrolled in this institutional ICD registry. The main problem was evaluating the occurrence of deaths occurring outside the institution because linking the national mortality registry with PAMI data yielded difficulty in identification and a time-lag when updating the databases. Despite these difficulties, PAMI is a comprehensive database that contains a vast amount of information . However, it not user-friendly since the data is disaggregated in many sources inside the Institution and is not accessible to the public.

5.1.4.3 Electronic medical record from private sector

In the private subsector, there are some institutions like Hospital Italiano de Buenos Aires with a well-developed Health Information System. It used electronic medical records of excellent quality. In this setting, a study evaluating the effectiveness of influenza vaccination in the elderly was performed. A retrospective cohort was developed and defined cases as those vaccinated. Researchers then assigned controls of the same age without vaccination (Garcia Marti, 2015). A propensity score was used to match the two arms of the study, and was possible because of a very detailed record of comorbidities. Hospitalisations and ambulatory resource use were compared between groups. This kind of study was only possible because hospitalisations and drug prescriptions were very well coded using standard classifications, something that it is not common in many other settings. Sometimes these kinds of studies are limited by a lack of human resources for the evaluation of data and the statistical aspects to be considered. However, electronic records like the one in this institution render it possible to generate high quality RWE in Argentina.

5.1.5 Conclusions

In general, Argentinian RWE is still in its infancy. Although some databases exist, data extraction and use is not coordinated or generalised. Issues regarding sharing data, linking different levels of care and codification are the main barriers.

5.2 Brazil

5.2.1 The Brazilian Healthcare System

All Brazilians and people living in Brazil have the right to healthcare (Cordeiro, 2004). To enable this, the basic doctrinal and organizational principles of the public healthcare system (The Unified Healthcare System – Sistema Único de Saúde - SUS) were defined in 5 articles (196 to 200) in the Brazilian Constitution (1998). The doctrinal principles are universality, comprehensiveness and equity. The organizational principles are regionalization, hierarchicalization, decentralization and social participation. Other infra-constitutional laws and regulations detail its structure, organization, processes and responsibilities. Following these principles, the Brazilian government is responsible for providing healthcare free of charge at the point of delivery. The SUS is funded by federal, state and municipal taxes. The healthcare is expected to be provided in an integrated manner from primary care to very specialized care (Cordeiro, 2004, Menicucci, 2009, Passero et al., 2016).

In a nutshell, primary care is the responsibility of municipalities, secondary and tertiary care are the responsibilities of the states, and the federal government is responsible for launching public healthcare policies. Furthermore, the government oversees specific national healthcare programs, such as vaccination, HIV, transplant, and 'expensive drug' programs (provide drugs free of any charge to all patients in need of expensive drugs), among others. Federal, state and municipalities have their own healthcare facilities, but they also contract the services of not-for-profit organizations.

In addition to the public system (SUS), Brazilians can seek care at private not-for-profit as well as for-profit organisations, and pay out of pocket for healthcare services and products. Citizens also have the option to buy a health plan or health insurance coverage to access a net of private healthcare providers (the supplementary healthcare system). The first health plans in Brazil were established in the 1950s when the auto industry plants were built in the southeast. In the past decades, there has been a continuous increase in the proportion of Brazilians enrolled in the supplementary healthcare system. In general, the perceived lack of adequate access to healthcare services and low quality of services are responsible for the increasing number of enrolees (Pietrobon et al., 2008).

The National Agency of the Supplementary Healthcare System was formally established in 1990. It is responsible for regulating and monitoring the supplementary system and its functions: healthcare plans and insurance companies, healthcare private providers and the rights and obligations of the enrolees (Pietrobon et al., 2008).

With a developing economy, Brazil faces the same challenges that other developing economies face: a huge demand for healthcare services and a lack of resources to satisfy all healthcare needs, both in terms of access and quality of services. Furthermore, Brazil's constitutional commitment to providing healthcare free of any charge to all raises another

challenge; there is no definition for what is considered state-funded healthcare (Ferraz, 2009). Given an increasing capacity to generate medical knowledge and innovation, once any healthcare product or service is approved to be commercialised (by the National Sanitary Agency - ANVISA), it becomes the right of Brazilians in need to use it, if prescribed by a physician. Due to economic constraints, it becomes a challenge for the public system (and even to the supplementary system) to provide access to all innovative technologies and quality services.

In 1994, the ministry of health launched the Family Health Strategy program with the objective to broaden access to primary care. Now, more than 60% of the population is covered by this program. However, scarcity of resources, including human resources, has been a barrier for the expansion and maintenance of this successful program (Montekio et al., 2011, Sousa and Hamann, 2009).

Both the public and the supplementary healthcare systems cover inpatient and outpatient services. Outpatient prescriptions are potentially free of charge at public pharmacies for Brazilians and residents in the country. In addition to the essential drugs list, there is an 'expensive drug' list available to patients free of charge, provided he/she has a physician prescription and complies with drug prescription guidelines. To be included in this list, pharmaceutical companies submit dossiers to CONITEC, a health technology assessment committee established at the Ministry of Health (Laranjeira and Petramale, 2013).

The Ministry of Health's "table of fees" used to pay private providers servicing the public system is outdated especially for the most common and unsophisticated procedures. For instance, a medical consultation is priced less than US$ 3. The same clinical consultation paid by a health plan or insurance company usually varies from US$ 10 to 40, and if paid out of pocket to private physicians it is usually priced between US$ 30 to 300.

Currently, Brazil has an estimated population of 207 million, and have the right to use the public healthcare system. Approximately 47 million people are enrolled and have the right to use the Supplementary healthcare system. However, in the past year, due to the severe economic crisis and the corresponding rise in the unemployment rate, approximately 1 million people lost their private health insurance plans (2016, Plans, 2017).

About 8% of Brazilian GDP is assigned to Healthcare (about 3.6% from the public and 4.4% from private sources - payment of health plans and insurance premium and out-of-pocked payments) (IBGE, 2015). It was estimated that the Brazilian government invested about US$ 59 billion in the public healthcare system for its 206 million inhabitants (US$ 0.78/day/inhabitant), while the 48 million Brazilians enrolled in supplementary healthcare system invested about US$ 79 billion (US$ 4.51/day/enrolee) in 2016 (2016 10 first months mean conversion rate - US$ 1.00 = R$ 3.5172) (Instituto de Economia, 2016). Both values are far less than the one needed to provide a full coverage and quality care to all citizens in need for healthcare. In fact, the supplementary healthcare system has a 4 to 5 times higher

investment per capita when compared to the public system. It may justify the perceived better access and quality of services and the preference Brazilians expressed to be enrolled in this system despite the additional premium to be paid by the enrolee.

Another important consideration is system inefficiency; despite its well-defined principles, inefficiency is entrenched through short-term decision-making. Also, a lack of prioritization, qualified data, information, knowledge and management skills amongst healthcare decision makers and managers contributes to inefficiencies. The mean tenure (SD) of Brazilian health ministers exemplifies this shortcoming; it stands at 15 (12) months for the past 20 years, a significantly shorter period than the mean tenure of 33 (18) months in the other 22 countries ($P<0.05$) (Ferraz and Azevedo, 2011).

In summary, although we can observe a continuous, but slower than needed, improvement in the Brazilian healthcare system, there is an urgent need to recognize the challenges country faces, the scarcity of resources that are available, to think and plan the Brazilian healthcare system based on a long-term perspective.

5.2.2 Real World Evidence: Overview in Brazil

The use of RWE has been advocated as a potential source of information to inform and influence decisions at the healthcare system level. In the Brazilian Healthcare system, as in any other country, a tremendous amount of health data is generated every day; however, the understanding and meaning of these data, their quality and potential applications to guide decisions vary and are constantly under discussion. In the past decades, due to the advances in information and communication technologies, the key challenge has shifted from simply obtaining and storing data to understanding what they mean, and how they can be applied to inform healthcare decisions. The real meaning of a simple healthcare indicator or resource, such as, a clinical consultation, may vary according to factors such as geography, setting and even the timing the data was recorded. This further complicates the use of data, information and the corresponding knowledge to inform healthcare decisions. It emphasizes the importance of defining of each data stream, a conscious understanding of the way it was gathered, for what purpose it was generated and what it will be used for.

Databases in Brazil, as in some other countries, are usually built for a specific purpose at conception. However, as they mature and become recognised, their use expands and goes far beyond their original purpose as a potential source of data to inform decisions. The need for decision makers to justify healthcare decisions can stimulate research using available databases or sources of information without a thorough check of a dataset's limitations and misconceptions, as well as how well sustained the quality was over the period it was gathered.

The use of available databases may not allow an accurate and evidence-based answer to a specific question posed, unlike prospective studies, in which a database can be built exactly to the scope that the researchers seek to investigate.

5.2.3 Examples of using real-world evidence

There are many healthcare databases in Brazil that can be used as a source of data and information for RWE. The most well-known and comprehensive one is DATASUS (tSUS database). There are also databases available at 2 national healthcare agencies: National Agency for Sanitary Vigilance (ANVISA), and National Agency for the Supplementary Healthcare System (ANS). Moreover, specific patient group registry data has been established and are positioned in various settings, for instance at the state and municipal secretaries of health, patient associations, pharmaceutical companies, service providers, proprietary hospital databases, and proprietary commercial diagnostic companies' databases provide informing RWE data. Furthermore, service providers, including health plan and health insurance companies' databases contain applicable RWE.

The aforementioned databases are limited in that they cannot be used to characterize the Brazilian healthcare system as a whole. Also, cross-use is limited by the diversity of data and the absence of common definitions of even the most well-known healthcare indicators. In addition, the quality of data varies, and they may even be inappropriate to use, especially when considering specific research questions posed.

Most of the available databases store isolated episodes of care. Others can describe in general terms only some epidemiological data and some aggregate population patterns of behaviour across time. Patient-specific data followed up over time with diagnosis characterization can be found only in a few public or private (for-profit and not-for-profit) hospitals and service-specific provider centres, but these tend to be proprietary data sources and are not readily available to the healthcare system.

There is also a big debate in Brazil about whether healthcare service providers should or should not provide an ICD-10 code to the ANS. As it stands, private service providers must supply data on services types and pharmacovigilance to the ANS as mandatory, in compliance with information exchange standards. Thus, data confidentiality surrounding further mandatory documentation of healthcare is an issue under discussion.

5.2.4 Challenges and Opportunities

Healthcare systems in many developing countries face a major challenge: how to meet the demand of 21st century healthcare and technology standards with funds that, as a percentage of gross domestic product (GDP), remain lower than what developed nations were investing in health in the 1980s. Furthermore, how can developing countries meet

these high expectations when they are still dealing with health problems that rich countries had overcome 40 or 50 years ago (Ferraz, 2006)?

In an environment of severe budget constraints and diverse healthcare needs, it is critical that healthcare decisions be based on the best evidence available. The correct understanding of the burden of disease, the judgement and prioritization of healthcare problems, the recognition of all resources available, including the characteristics and quality of the workforce healthcare team are imperative for the correct establishment of public policies for the short- to long-term, and for the planning and implementation of actions to satisfy the population's minimum healthcare needs.

Country-level data and information is a key element in the process of identifying a population's needs. It is needless to point out that the quality of the data, the recognition of intrinsic limitations and its correct use will determine the chance of success of progressively reaching the desired healthcare objectives. In this sense, the appropriate use of RWE does play a vital role in developing countries. Not only morbidity and mortality data is essential to determine and monitor over time the burden of diseases, but also to allow a clear understanding of the healthcare gaps that are usually observed in healthcare systems. It is also important to point out that the process of information and knowledge generation should start with a well-posed and relevant question that can be justified based on biological, economical and/or social grounds.

RWE derived from various sources such as health records (electronic or not) can be viewed nowadays as a complement of the knowledge generated and gained from the traditional and prospective research designs. This includes sources such as public and private databases, claims and billing data and even from personal devices, and health related apps that monitor daily defined outcomes, among others.

The main challenge a developing country like Brazil faces is to identify the most important and relevant research questions that RWE data collection should answer. As large amount of data sets of uncertain quality are available, it is possible some well-known methodological tools are not adequately used, especially by non-experts. A lack of minimally-qualified researchers, or the indiscriminate use of data without critical quality appraisal can jeopardize the credibility of the results and corresponding conclusions.

RWE can be a valuable tool to generate hypotheses for better planned and prospective studies; it can provide insights about the effectiveness of preventive strategies, the discriminating power of a diagnostic tool, or the effectiveness of treatment options in a wider sample of patients with varying social, economic and biological characteristics. It can also be used to fill the information gap in modelling studies, notably, the economic evaluation studies. The opportunities for RWE uses are extensive, especially if we consider that most of the studies in global literature that attempt to evaluate new healthcare strategies or programs are implemented in the developed world. Although these studies tend to be

internally valid, they may lack external validity as the population characteristics enrolled may differ from those in developing countries. Essentially, RWE has also the potential to unveil aspects of real world care and patterns of healthcare resource use.

Developing countries like Brazil face many challenges when potentially using RWE, but at the same time, the need for useful information and high-quality evidence to guide and justify healthcare decisions is critical. In this scenario, it should not be allowed to disregard any piece of qualified data or information that could enable decision makers improve healthcare systems step by step. Current information and communication technology makes it relatively easy nowadays to study different sets of data from diverse sources. Consequently, there is a need and opportunities for improving, maintaining and managing appropriately existing databases and other data sources, as well as building new ones that are reliable, complete and that contains qualified data.

5.2.5 Existing Key Data Assets

5.2.5.1 DATASUS (The database of the SUS)

DATASUS was established in 1991 as the National Foundation of Health (FUNASA) was created. Initially its main objective was to control and process the payment of services to public and private service providers for the SUS. DATASUS later took responsibility for collecting, processing, and disseminating healthcare and demographic data. These included indicators, services and products consumed as well as some estimates of mortality and morbidity across specific populations. For the past 26 years DATASUS has developed more than 200 information systems to better inform the Ministry of Health, as well as the state and municipal secretaries of health. Some examples of these specific systems and programs are: SUS hospital information system (SIHSUS), SUS outpatient service information system (SIASUS), Primary Care Information System (SIAB), National Immunization Program information System (SI-PNI), Pregnancy Follow-up Information System (SISPRENATAL), Hypertension and Diabetes Registration and Follow-up Information System (HIPERDIA), and National Health Facilities Centers (CNES), among others (Datasus. Departamento de Informática do SUS, 2017).

5.2.5.2 SUS hospital information system (SIHSUS)

The SIHSUS was established in 1981 before SUS was defined and was its first information system. Its main objective was to register and reimburse the hospitalisations of patients cared by SUS in public, not-for-profit and for-profit private hospitals contracted by SUS. Depending on the type of hospital, the reimbursement can be based on annual budgets, contract based on minimal volumes, or based on a SUS table of fees. The payment based on a fee-for-service or list of consumed items is only eventual (Datasus. Departamento de Informática do SUS, 2017).

5.2.5.3 SUS outpatient service information system (SIASUS)

The SIASUS was created in 1992 and made progressively available after 1994 with the main objective to reimburse the provision of outpatient healthcare services (Datasus. Departamento de Informática do SUS, 2017).

5.2.5.4 Other databases

The SIAB is strategically linked to family health programs, and routinely collects family demographic data, housing and sanitary living conditions, health states, composition and organization of family health teams as well as the services provided. It is the main monitoring, follow-up and management system for family health across the country (Datasus. Departamento de Informática do SUS, 2017).

The SI-PNI was developed to evaluate the risk of an epidemic for the managers of the national programme of immunization. Risk data is based upon the rates of vaccinated target groups by age and geographic area. Besides this health data, it also allows a close control and management of stock and distribution policies of immunobiological (Datasus. Departamento de Informática do SUS, 2017).

The SISPRENATAL has followed up data of more than 3 million pregnant women in over 5000 Brazilian cities. It is linked to the prenatal and childbirth programs and helps health teams to provide at least the minimal services and products that pregnant women require for adequate prenatal care. Also, an institutional objective is to study factors that contribute to decreasing in the rates of maternal neonatal and infant morbidity and mortality (Datasus. Departamento de Informática do SUS, 2017).

The HIPERDIA allows the registration and follow up of patients with hypertension and diabetes mellitus treated at SUS. It allows the public system to know the demographic and epidemiological characteristics of this population, morbidity and mortality patterns as well as the adherence to the treatment programs proposed for the patients. It also allows a close control and management of stock and distribution policies of hypertension and diabetes drugs (Datasus. Departamento de Informática do SUS, 2017).

The CNES is the national register of healthcare providers. It presents updated information about the providers, their installed capacity, availability of services, equipment, medical specialties offered and the characteristics and expertise of the whole healthcare team workforce (Datasus. Departamento de Informática do SUS, 2017).

Only recently, in 2011, the Ministry of Health established a regulatory ordinance that created the National Health card. Each Brazilian is now supposed to be registered and have a unique identification card that will be used across the country both at the public and private healthcare system. Its implementation, however, is facing some challenges and not all

Brazilians (even the ones who rely only on the public system) do already have a card (Ministério da Saúde, 2011).

In addition, there are some barriers and difficulties to feed the DATASUS system. As the incentives to regularly register the data are not clearly defined and the enforcement sometimes does not exist, some patient encounters are simply missed.

Finally, a recent study completed in Campinas (a city that is about 100 km from São Paulo) to assess the percentage of the population registered by the community primary care agents and that have a National Health Card number, reported that only about 50% of population had been registered. The authors also observed a considerable percentage of individuals that were incorrectly registered. The most commonly observed errors identified were incorrect demographic data (Santos et al., 2017).

5.2.6 Conclusions

In conclusion, the exponential increase of knowledge in the life sciences field, specifically in health sciences, in the past few years has increased complexity in decision and implementation of health care system strategies. Despite decreased uncertainty when making health care decisions due to the advancement in scientific methods, and despite the asymmetry of information, knowledge and power to make decisions, the importance of individual preferences is being recognised. As the sole recipients of interventions, patients are more than ever able to take an active role in the healthcare decision-making process. Health care stakeholders are now in a position to recognize the scarcity of resources available and the ever-increasing amount of knowledge. Interventions to improve the population's quantity and quality of life should therefore be designed to address and discuss health care issues that will guide critical choices and define health care priorities based mostly on judgment and the best evidence available (Ferraz, 2015).

5.3 Chile

5.3.1 Healthcare system in Chile

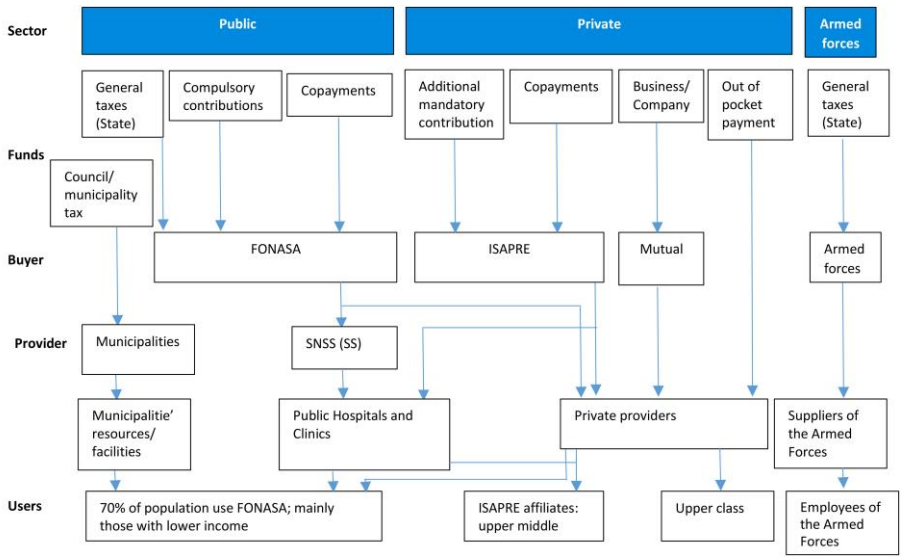
The Chilean healthcare system based on insurance, with combined public and private funding and provision of services, making it a mixed system. At the upper level, the Ministry of Health oversees the system, and the Superintendence of Health is the regulatory entity for public and private insurances and providers. Meanwhile, the Institute of Public Health is the regulatory institution for drugs, medical devices as well as the national reference centre for diagnostics. The healthcare provision in the public sector is managed by 29 autonomous Health Services, which altogether are called National System of Health Services (SNSS) and the Municipal Primary Care System. Public health providers can purchase health commodities through the National Centre for Supply (Central de Abastecimiento, CENABAST), which is responsible for central procurement. In the private sector, private

health clinics, medical healthcare facilities, laboratories and pharmacies provide health services.

In Chile, people can be insured in either public or private sectors. The National Health Fund (FONASA) is the public insurance, which covers approximately 70% of the population, including the rural and urban poor, the lower middle class and retirees, as well as the better-off professionals and technicians who choose to join it. The relatively wealthier beneficiaries of FONASA can choose to receive healthcare from private providers, often with higher co-payments. Occasionally FONASA is forced to contract services from private providers to meet legal guarantees, which have not been covered in the public sector because of high demand (Becerril-Montekio et al., 2011). The public sector is financed by general taxes, mandatory contributions and co-payments collected by FONASA. On the other hand, in the private subsystem the insurance is provided by Health Insurance Institutions (ISAPREs), which is funded by compulsory contributions of employees who choose one of these companies. ISAPRES covers approximately 17.5% of the population in the highest income social groups. Because ISAPRES sells health plans, in many cases, people choose to increase the contribution through voluntary top-ups to get access to a better plan. In principle, every citizen has the right to choose insurance in the public or private system; however, in practice only people with higher income, healthier and younger have access ISAPREs.

In addition, about 10% of the population is covered by other public agencies, mainly the Health Services of the Armed Forces. Independent workers may choose to affiliate with FONASA or some ISAPRE, or may lack any social health insurance coverage (Becerril-Montekio et al., 2011).

Figure 4: Schematic view of healthcare system in Chile



Source: (Becerril-Montekio et al., 2011)

5.3.2 Real World Evidence: Overview in Chile

Chile has significantly improved its data and registries, increasing its capacity to undertake RWE. However, the extent to which the country systematically uses the RWE based on these data is limited. In terms of registries, Chile's Ministry of Health launched a Digital Strategy in Health in 2008, whose objective was to coordinate actors of the health system to share information in a structured and organized manner. One of the main products was the Information System of the Healthcare Network (Sistema de Information de la Red Asistencial, SIDRA), which aims to create a national repository of health information and a common electronic medical record. Both resources would help patients navigate through the health system improving efficiency and satisfaction. In addition, the system – when implemented – will provide a major source of RWE and an opportunity for enhancing national health statistics, monitoring performance of the health system and improving national planning.

This initiative is led by the MoH, which coordinates the implementation of activities, without infringing on the autonomy of the country's public services (primary care services, hospitals, etc.). In the first stage, the MoH encouraged the implementation of information systems to register population data under controlled conditions the primary care, emergency consultations, reference and counter-reference mechanisms, pharmaceutical delivery, and medical agenda. Nevertheless, despite efforts made by the authority in the last few years, an important challenge persists; the actors of the system need align to reduce the variability in information systems that are implemented. Synchronicity of systems would enable the effective articulation of information. Because of service-sector autonomy, some systems have been implemented that cannot be integrated with the rest.

On the other hand, Chile has some well-institutionalized registries that provide very relevant information that monitor the performance of the health system. First, demographic data on mortality, birth rates and fertility are reliable and publicly available. Second, the hospital discharge database is a country-wide hospitalizations census for particular periods. Third, Diagnostic Related Groups (DRGs), which are available in an increasing number of hospitals in Chile, provide an important source of information to characterize the case mix of hospitals and improve the financial management. Fourth, the system for the management of explicit guarantees (Sistema de Gestión de Garantías Explícitas, SIGGES) records information related to the services provided by the Chilean health benefit plan. Fifth, data about the utilization of services in the public (REM) and private sector (REMSAS) are also available from the Department of Statistics in the MoH (Ministry of Health, 2017).

In addition, Chile collects information regularly through population surveys, which are all made publicly available. Some examples are: National Health Survey (2003, 2013, 2016); National Survey of Food Consumption (2014); Patient Satisfaction Survey (2012); National Survey of Quality of Life (2000; 2006); Socioeconomic characterization (every 2-3 years

since the 1980s); Households budget survey (2012, 2007, 2203); and the National survey of breastfeeding in primary care (2013).

5.3.3 Legal and standard practice frameworks

The law on “duties and rights of patients” regulates the use of information collected from patients in Chile. This law forbids the access to medical records by any person or institution not related to the care of the patient, which includes researchers. The only way to have access to medical records is through explicit legal authorization of the patient, his/her legal representative, or his/her direct inheritors in case of death. In cases of intellectual disability, where patients can express their will, their consent can be taken into account as long as there is an authorization of the health authority and the corresponding ethical committee. When patients cannot express their will, their information cannot be used. If information is used without these authorizations, the researcher can be suspended up to 3 years of professional practice, and completely suspended in case of repetition (Ley 20.584, 2012).

However, the law allows institutions of the health system (MoH and its dependent institutions) to have access to these records to produce information relevant for public health decisions such as follow up, monitoring, planning and audit. Therefore, if researchers ask a public institution, the data can be released as long as the research is conducted to reveal information that will be useful for the continuous improvement of population health. Furthermore, their publication is allowed insofar as the relationship between data and identity of people cannot be revealed (Ramos and Arenas, 2013).

5.3.4 RWE in practice

Regulatory decisions for commercialization of pharmaceuticals and medical devices in Chile are centralized in the Institute of Public Health. The Chilean law establishes a strict process for authorization of pharmaceuticals and much less rigorous for medical devices. Likewise, pharmacovigilance is more developed than techno-vigilance, which might change with a new law that sets up a new registry process for medical devices. Nevertheless, in the current situation RWE has a role in informing safety after the drug is commercialized. The National Centre of Information of Pharmaceuticals and Pharmacovigilance is the institution in charge of gathering information on adverse drug reaction and, from there, to generate the alerts as well as withdraw drugs from the market.

In Chile, Health Technology Assessment is performed partially by the Ministry of Health (MoH) to evaluate evidence about efficacy and safety, mostly to inform the elaboration of clinical guidelines. However, although economic evaluation is desirable for coverage decisions and the MoH has produced a methodological guideline to produce it, the use of economic modelling has been rarely considered to inform such decisions. More recently, Chile has launched a law to fund high cost drugs, for which a new and more comprehensive

HTA process has been set up (Ley 20.850, 2015). Although there is no a new institution responsible for this, the new system defines a more structured process for coverage decisions and it requires economic evaluation as one of the inputs. In response to the law, an increasing number of economic models have been produced, which has improved the capacity in the country to develop this type of evidence.

Therefore, given these recent changes in the Chilean coverage system, it is expected that more RWE will be produced and used in the following years for HTA. Meanwhile, economic evidence is currently being produced mostly with international data, though good local registries can be used to estimate cost and resource use locally.

Chile has significantly improved its capacity to develop clinical guidelines since the implementation of the health benefit plan GES (explicit health guarantees) in 2005. The priority setting undertaken was structured such that a defined number of health problems are included in the plan with explicit baskets of services. In addition, for each health problem the health authority produces a clinical guideline driven by the principles of evidence based medicine. However, most of the evidence considered in guidelines is foreign given the lack of RWE produced in the country.

As mentioned before, coverage decisions in Chile have rarely considered economic evaluations such as cost-effectiveness analysis. However, the health authority needs to estimate the budget impact of an innovative technology, which is used to inform decisions for coverage. Unfortunately, this exercise is not public or transparent and the extent to which it determines the priority of one technology against another is unknown. In terms of pricing, the Chilean health authority cannot negotiate or regulate prices, which is legally forbidden. In this context, the Chilean public health system buys through public procurement, for which no RWE is used.

5.3.5 Challenges

Chile has made significant efforts to increase and improve its records and information systems. Indeed, as a member of the OCDE Chile has sought new and better registries to enhance its estimates to share with the international community, many of which are used to inform local decisions. However, it still faces several challenges to maximize the value of RWE in the actual job of the health system.

By far the most ambitious goal of the Chilean health system is the SIDRA project. It aims to generate an integrated information system that connects primary with the secondary and hospital level care, providing longitudinal data about care supplied in the health system but also about outcomes achieved by patients. Unfortunately, SIDRA has faced many barriers to implementation, mainly because local health systems, either primary, secondary or hospital level, started operating their own information systems before SIDRA was launched. In addition, SIDRA is a coordination program, but it does not provide additional resources to

unify information systems across the country. Hence, investments are the responsibility of local jurisdictions. In this context, the central health authority will face the challenge of harmonizing records, forms, processes and information systems as well as providing additional resources to cover transaction costs associated to changing from one system to another. These transaction costs not only include new software but also training, planning and coordination.

In terms of regulation of medical technologies, the country urgently needs to improve systems for pharma and techno vigilance. For example, there are some areas where surveillance is very limited as in the use of narcotic drugs. However, Chilean pharmacies have a legal obligation to retain prescription data, which are also shared with the Institute of Public Health. There is no a periodic utilization analysis of these drugs. In fact, there is no training or incentives for health professionals to communicate the adverse effects of drugs, and notification to the authority is voluntary.

The production of information from data is limited because of limited resources, both professional and financial. Most of the analyses of this data type requires trained human resources, which in Chile are mainly located in universities and academic centres. Unfortunately, funding for analysis of these records through research grants is limited. Although the MoH has some departments dedicated to analysing relevant data, its capacity is very limited and usually contracts out these services to local research centres, despite also being constrained by a small budget.

5.3.6 Opportunities

The objective of achieving a national repository of health information should be maintained in the policy agenda. Despite the difficulties of implementing SIDRA, the health authority should persevere with the initiative. Opportunities to improve the rather small achievements accomplished are surely linked to the additional resources and policy instruments that endow the MoH greater power to implement this initiative.

The health authority should focus its efforts on identifying relevant questions and translating RWE into health policies, but it should not spend time and effort in producing evidence. In contrast, it should communicate its work to other public institutions –such as those assigning funding for research to produce relevant information. In addition, the health authority should publish methodological guidelines for the collection and analyses of RWE, guidelines would facilitate and encourage the production of studies.

In health technology assessments, the main opportunity is to set up a centralised national process, ideally a new institution. This would increase demand for clinical research, systematic reviews, economics evaluations and patient reported outcomes. If the health authority is committed to assessing evidence for its decisions, the third sector activates capacities to produce this evidence. In addition, private industries –pharmaceutical and

medical devices- would invest more in generating this required evidence instead of marketing or other practices to improve access.

5.3.7 Examples of using real-world evidence

5.3.7.1 RWE to examine Health Inequalities

Health inequalities have received broad attention in Chile. In 2012 Parage and Vasquez studied the impact of the Chilean health reform on the use of medical services in Chile using both CASEN surveys 2003 and 2009 (Parage and Vasquez, 2012). Their findings suggested that the increase in the average use of services were not always associated with equity improvement. Likewise, Cabieses et al. (2015) explored whether socioeconomic inequality in self-reported health (SRH) fell after the Chilean reform. They also used CASEN survey from the 2000 to 2013 to examine the magnitude of inequalities in SRH over time, and the contribution of both, legitimate and illegitimate factors, to this magnitude using concentration indices (Cabieses et al., 2015).

In both cases, the analyses were performed using a national representative sample of more than 300,000 people. Both the large number of variables related to socioeconomic status and the size of the sample enabled the characterization of inequalities and exploration of relevant associations among variables. One disadvantage was its cross-sectional nature, which limited analyses for causal inference.

5.3.7.2 RWE to examine out-of-pocket expenditure

Another topic of main interest in Chile is out-of-pocket expenditures. Several authors have examined the household budget survey in different periods. For example, Cid and Prieto (Cid, 2012) carried out an analysis comparing surveys from 1997 and 2007. Later, the Ministry of Health examined the same survey, but included the more recent 2012 survey (Ministry of Health, 2015). The more recent data showed that around 6.3% of the household expenditure was out-of-pocket health expenditure, and 4% of the Chilean households incurred in catastrophic expenditure.

The survey is a national representative cross-section study, where one-month household expenditure was collected from more than 13,000 households alongside one year of data collection. This data is very rich in terms of the description of the items families purchase during that month, which allows researchers to disaggregate different health care items, for example, drugs, co-payments, etc. In addition, the data is regularly collected in the country, which allows cross-sectional comparisons. Like the CASEN survey, these comparisons between periods are limited because they do not survey the same households. However, the large sample size mitigates this limitation.

5.3.7.3 RWE to examine performance of health system

Finally, another area of interest in Chile is the performance of the health system in the public versus the private sector. Cid et al. used the national hospital discharges database to explore potential differences among health providers in mortality due to acute myocardial infarction and stroke. They showed a lower rate mortality in the private sector, which provided interesting evidence to judge inequalities in Chile (Cid et al., 2016).

This type of research is highly valuable in Chile, but poorly explored. Although this database is very rich because is a continuous census of private and public hospital discharges, it is demanding in terms of data management and is limited to performance indicators. Other data to explore performance is probably available at the local level (hospital, primary care health centres), which makes it more difficult for researchers to have access. In addition, few incentives have been generated from the health system to encourage researchers to invest more time exploring those sources of evidence.

5.3.8 Conclusions

Chile has history of important achievements in public health, driven by rational decisions based on scientific information, mostly epidemiological observational studies. Although the country has captured good health indicators, it still faces very important challenges that obliges responsible planning, monitoring and fair decisions about allocation of limited budgets. In this context, the use of RWE seems essential to provide health planners the most relevant information to make their decisions.

Although, there is capacity to conduct RWE research in the country, this is limited by: first, the scarce resources allocated to fund RWE research; second, a lack of good quality sources of information in all relevant areas; and third, the lack of stewardship of the MoH to drive the production of relevant evidence. In the near future, we expect a marginal increase in public resources for research and a gradual improvement in the current information systems. However, there is a big opportunity for the health authority to articulate efforts with other public institutions as well as providing signals to activate the development of research with RWE with private funding.

5.4 Colombia

5.4.1 Healthcare system in Colombia

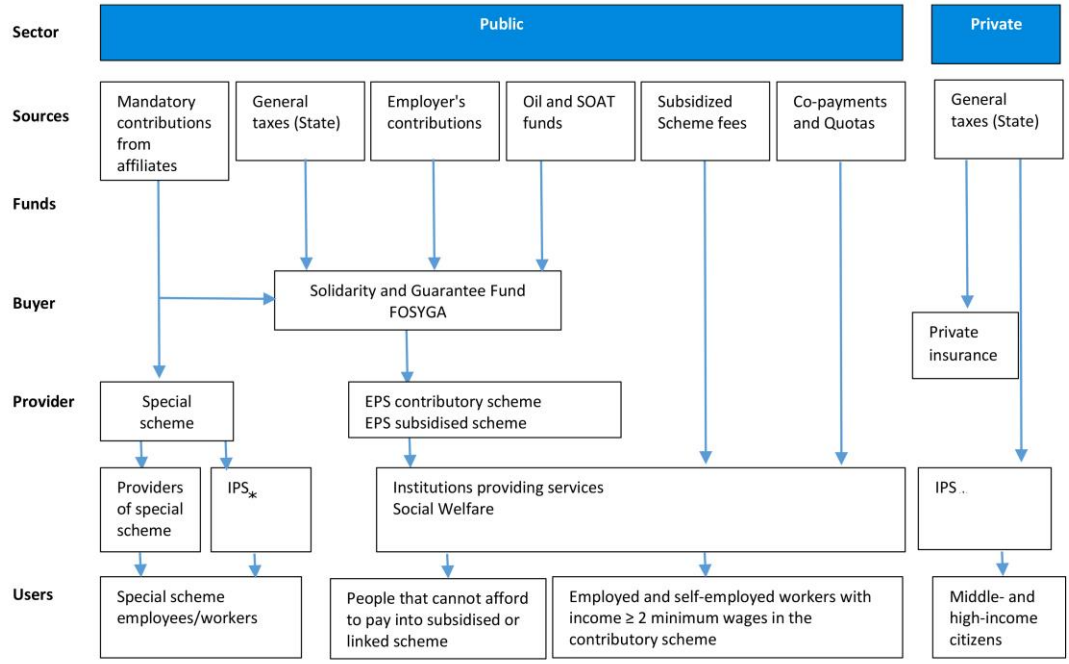
The Colombian health system has been organized as a public service, where the population is guaranteed access to services and financial protection through social insurance. The architecture of the Colombian health system promotes the specialization of functions amongst its actors. It is also characterized by public/private insurance, the provision of

healthcare services, and a regulated market to achieve higher efficiency and quality of performance. (Giovanella et al., 2012)

The Colombian health system is made up of a large social security sector and a declining private sector. Its central axis is The General System of Social Security in Health (SGSSS). The SGSSS featured 67 organizations, 24 of which operated the contribution scheme, and 49 acted in the subsidised scheme. Six of them served both schemes. The contribution scheme combines salaried, pensioners and self-employed workers with income equal to or greater than a minimum wage. The subsidised scheme covers everyone who cannot afford to pay in. In 2010 the private and public insurance coverage was 39.7% and 51.4% of the total population, respectively. The Special scheme covers independent health systems for the military, teachers, employees of the Colombian oil company and other organizations. The Special scheme has the autonomy to determine their coverage and service structures (Giovanella et al., 2012, Guerrero et al., 2011).

In 2010, only 4.3% of the population remained outside the social security system. The contribution scheme operates based on a quota from its affiliates. The special scheme has its own financial mechanisms. Membership of SGSSS is mandatory and is made through public or private health promotion entities (EPS), which are responsible for offering at least the Mandatory Health Plan (Plan de Beneficios en Salud). The EPS deliver the collected funds from the contributions to the Solidarity and Guarantee Fund (FOSYGA), and retains (or receives back) the amount equivalent to the unit of payment per capitation (UPC) adjusted for risk, according to the number of affiliates they have. The providers of care are the service provider institutions (IPS), which may or may not be integrated into the EPS, but in any case are contracted by them. The exclusively private sector is used predominantly by the middle to high/high income class that, still quoting in some EPS, contracts private insurance or goes to the private practice. A portion of the middle-income population, for lack of coverage or for not having timely access to the SGSSS, is forced to attend the private consultation making payments out of pocket (Giovanella et al., 2012, Guerrero et al., 2011).

Figure 5: Schematic view of healthcare system in Colombia



*Service provider institutions (IPS) are both public and private
Source: (Guerrero et al., 2011)

5.4.2 Real-world evidence: Overview in Colombia

With universal coverage as one of its main objectives, in 1993 Colombia had a drastic reform of its whole healthcare system (Merlano-Porras and Gorbanev, 2013). It was clear since its inception that appropriate information systems were essential for a complicated network of both private and public healthcare providers and healthcare insurers competing with each other (Bossert et al., 1998). This competitive environment has led to the closure of many (mostly public) inefficient hospitals. Those with poor information systems were particularly affected (Bernal-Acevedo and Forero Camacho, 2011).

Even before the 1993 health reform, Colombia had developed a relatively good tradition of government-led information systems. The DANE (National Statistics Administrative Department), created in 1953, has had since its inception the role of generating statistical data in many fields, some of them particularly relevant for health decision-making. These include demographic data, family information and several determinants of poverty. Coverage of death certificates has been considered excellent, not so much in the information on the cause of death as in age, gender and place of death (Rosselli et al.) Due to legal consequences, external causes of death have been well registered, and have been used for important political decisions (Rosselli et al., 2017).

Apart from the official national census (the last one dates back to 2005), Colombia has had a tradition of large door-to-door national surveys. One example is the National Mental Health

Surveys, which have been done in 1993, 1997, 2003 and 2015. There are also National Oral Health Surveys, as well as child health household studies, done by the Colombian Institute of Family Welfare (ICBF), or the SABE set of studies with senior citizens (Cano-Gutierrez et al., 2015). The single-payer healthcare system has also favoured the growth of large pharmacy management systems like Audifarma which, by 2010, handled the prescriptions of 4 million Colombians (Machado-Alba et al., 2010). Their databases have been extensively used to describe nationwide prescription patterns and to detect possible prescription errors (Machado-Alba et al., 2016).

5.4.3 Challenges and opportunities

The long-standing tradition of keeping registries is finally bearing fruit. The data collected is not always complete, and has quality issues that need to be addressed. The capacity of decision makers, including government, insurers, and health providers, to analyse all this information is not yet enough. Most of the governmental publications are thick grey documents, full of tables and raw data, with very superficial analysis of geographic distribution and age groups at most. Data, however, are freely accessible for any research group interested in further statistical analyses, which brings about confidentiality issues (Gamboa-Delgado and Rodríguez-Ramírez, 2014). The use of all these databases in the decision-making process is just beginning.

5.4.4 Existing key data assets

In Colombia, cancer registries started in 1962 in the city of Cali (Cendales et al., 2012), by then it was the only organized cancer registry in Latin America (Pineros et al., 2006). This effort was followed later by other Colombian cities, like Bucaramanga, Manizales and Pasto (Alba, 2016). These 4 registries have been the basis for official national cancer incidence and prevalence figures, reported to the International Agency for Research on Cancer, IARC, in France (Pineros et al., 2006, Alba et al., 2016, De Vries et al., 2016). These registries imply a lot of work just to keep them updated, but their analyses and the peer-reviewed literature based on them is yet quite low.

The Colombian National Institute of Health (Instituto Nacional de Salud, INS) started in 1999 a nationwide system of disease registries with relatively good quality, with a list of medical conditions with importance in public health (López, 2009). This compulsory registry is called Sivigila, and includes vaccine preventable diseases, vector transmitted diseases, tuberculosis, leprosy, sexually transmitted diseases, HIV/AIDS, zoonosis, ophidian accidents, intoxications, and chronic diseases (diabetes, cancer, cardiovascular disease). A number of papers (Zarante et al., 2016, Ramirez et al., 2014) have used this information and assessed its validity. Most publications by this group from the INS are thick reports with lots of tables but only superficial analysis.

The most ambitious information system in Colombia is the SISPRO project (Sistema Integral de Información de la Protección Social, www.sispro.gov.co), which keeps a registry of every contact a person has with the health system (314,458,594 contacts in 2014 alone) (Rosselli and Hernández-Galvis, 2016). For each contact, the place where the service is provided is registered, the age and gender of the patient, the service provided and the main diagnosis, according the ICD-10 classification, together with the patient's ID number. The accuracy of this diagnosis has been questioned, but apparently data tend to be better for high cost diseases (or procedures), since reimbursement will depend on it (Jiménez-Pérez et al., 2015). Many research groups are now using the SISPRO information, and the number of papers based on it will very probably grow in the years to come.

As part of the SISPRO project, in 2007 the Ministry of Health created the System for Information on Medication Prices SISMED (Sistema de Información de Precios de Medicamentos), which reports all the nationwide medication sales. Presentations, volumes and prices are all reported in this free access system, after registering in the SISPRO web page (Ministerio de Salud y Protección Social). There are not many examples in Latin America of local market share and cost data, which end up being very useful in modelling exercises or for budget planning.

5.4.5 Conclusions

Colombia inherited the Spanish tradition of keeping registries, first for the religious administration of parishes, then for governmental bureaucratic purposes. Health related information has been collected for decades, and the 1993 health system reform imposed a need of even better information systems. The field of health economics has profited from this, since we can use simulation models or produce budget impact analyses with local epidemiologic, clinical and cost data. Human resources, yet insufficient and perhaps concentrated on universities and consultancy firms, will help the government and other stakeholders in incrementing the use of this information for intelligent decisions

6.0 Conclusions and Discussion

6.1 Overview of real-world evidence in the global context

The use of RWE is growing globally and the development of observational and registry-data research benefits all stakeholders of the healthcare system. Payers benefit from cost-efficiencies, regulators from increased opportunity for surveillance and ability to implement monitor quality of care, clinicians from enhanced clinical practice and the pharmaceutical industry from targeted R&D and optimized HTA submissions.

RWE and related studies are, in themselves, not new; after all, researchers have been conducting chart reviews for years. However, this type of study has been gaining renewed interest over the last decade. According to a recent estimation, ClinicalTrials.gov had listed 968 studies with the term “real world” by early 2017. The number of real-world studies conducted in the last six years totalled 700, compared to only 258 in the 2000s, and just seven in the 1990s (Barham).

The abundance of RWE in the US and Europe is may be due to the way healthcare systems are structured and legal frameworks that endorse the accumulation of routine clinical. The US is one of the countries where numerous data resources exist and can be used for such studies as the collaboration models are based on the commercialization of data assets. In Europe, the situation is more diverse; for instance, in the United Kingdom and the Netherlands data availability is also based on a transactional model similar to those of the US. While in France and the Nordic countries, data assets also abound, they have not been commoditized and thus access is free of licensing costs but contingent on the approval of the research plan. Databases or records from these countries are deemed acceptable by local experts (Hughes and M., 2013). Solutions in the rest of Europe are more diverse as is the quality of those data resources. Anyhow, initiatives like adaptive pathways and experiences of research programs enriched in joint or parallel scientific advice encourage other European countries to use RWE in their decision-making.

In this White Paper, we have classified the types of RWE data sources and studies, shown how they can help in improving different types of policy decisions, outlined the methodological and practical challenges. We have also identified numerous uses that different stakeholders have for RWE.

Regulators in Europe and the US are found to be using RWE for pharmacovigilance, in early-access schemes such as adaptive pathways, compassionate use programs, and others of the like. HTA bodies and payers rely on RWE is models, dossiers, conditional reimbursement schemes and innovative pricing models. Clinicians and other healthcare providers consult RWE to inform the interpretation of international guidelines (usually based only on data emanating from RCTs) especially when transferability may be an issue in certain countries or regions. Patients trust that RWE best captures measures of real benefit

or harm that matter to them in real life. The biotechnology and pharmaceutical industries count on RWE to demonstrate value of the healthcare interventions they have already developed, but also to optimize their R&D investments and maximize revenue. Overall, well-informed decisions benefit the healthcare system as a whole with gains in transparency and reducing uncertainty.

6.2 Conclusions from the case studies

Table 8 summarizes the key findings of four case studies and presents the main takeaways in terms of the framework of each healthcare system, use of RWE, challenges, opportunities, and a selection of country-specific data assets.

6.2.1 Use of real-world evidence: state of affairs

Some Latin American countries use RWE more than others and is especially noticeable from a regulatory perspective which considers RWE only for auditing purposes. This is the case in Chile, while in other cases not at all. Regulators in all four countries strictly adhere to the traditional evidence hierarchy with RCT data as the golden standard, thus considering RWE substandard and relegating it to an insignificant role.

In Brazil, Chile and Colombia RWE is commonly used in HTAs (Gregory et al., 2014), but Argentina was found to be lagging behind in this aspect. Yet, new regulations on the compulsory assessment of high-cost interventions may offer an opportunity for a better exploitation of the potential of RWE in the country. In all four countries, other stakeholders such as health insurances, health care providers and the pharmaceutical and biotechnology industry also have isolated experiences of using RWE in price negotiations but mainly in the private sector.

6.2.2 Challenges

Each country faces multiple challenges related to RWE generation and use. The key ones are summarized below:

- Problems with the data. There is a wide variety of available data across all Latin American countries. Though, key challenges countries are facing pertain to data integrity, quality and security. National variations in data collection, patient concerns in sharing data and rapidly shifting landscape pose a serious challenge to gather meaningful insights from data.
- Gap in expertise. Brazil, Chile and Colombia pointed out that there is lack in skilled personnel to analyze the data. To benefit from the RWE knowledge, all interested parties must address this gap and engage in capacity building.

- Trust Issues: There is limited, not-always transparent and complex collaboration of various parties (pharma, academia, hospitals, government, payers). Data security issues and limited access affects the opportunities to analyze the data and utilize the knowledge. In turn, this reinforces another difficulty regarding the longitudinal follow-up of patients through the different healthcare services.

6.2.3 Opportunities

An increased use of RWE has been advocated for by academia and the pharmaceutical industry; fostering other potential users to generate the data and use results. In our case studies, we identified some common opportunities to improve the use of RWE:

- The region has witnessed an extension of healthcare coverage in at least two dimensions (bigger population and more diseases/interventions covered) which exerts pressure on healthcare budgets. Thus, there is agreement on the need to more closely monitor results, particularly those pertaining to high-cost interventions.
- Data registration is improving in all the countries with a variety of strategies to address specific issues. We have identified initiatives to extend the use of EMRs and improve registration (e.g. harmonize coding systems and languages, minimize the use of free text, train personnel on coding systems, etc.) and to improve the traceability of patients and allow for longitudinal follow-up (e.g. systems integration, central authorities aiming at extending data consolidation, etc.).
- The rapidly growing number and maturing HTA units in the Ministries of Health and independent HTA agencies in the region.
- Various types of HTA institutions and units in Latin America and the increasing adoption of pharmacoeconomic guidelines as well as evidence-based healthcare policy design represent a promising prospect for the extended use of RWE in the region.

Table 8: Summary findings in Latin America

	Argentina	Brazil	Chile	Colombia
Healthcare System	✓ Highly decentralized. Three sectors (public, private and social security) each very fragmented ✓ Multiplicity and diversity of stakeholders and decision makers	✓ Highly decentralized (primary, secondary and tertiary levels) ✓ Public healthcare is universal and free for everyone ✓ Provided by both private and government institutions	✓ Mixed and based on insurance, with a combined public and private funding and provision of services	✓ Organized as a public service, where the population is guaranteed access to services and financial protection through social insurance
Use of RWE: state of affairs	✓ No use by regulators ✓ Limited use in HTA, which is non-binding ✓ Limited use in coverage decisions is starting ✓ Main promoter of RWE use is the pharmaceutical industry	✓ Multiple sources for RWE ✓ Multiple users (government, insurance, pharma) ✓ Commonly used in HTAs ✓ ✓	✓ Used in HTAs (clinical and economic) ✓ Implemented data collection system(s) is expected to provide a major source of RWE and an opportunity for enhancing national health statistics, monitoring performance of the health system and improving national planning ✓ Well-institutionalized registries provide relevant information to monitor the performance of the health system ✓ RWE has a role in informing safety after commercialization	✓ Used in health decision-making (DANE) ✓ Multiple national or large-scale surveys (national survey, large door-to-door national surveys, National Oral Health Surveys, child health household studies) ✓
Challenges	✓ Legal and standard practice barriers: Difficulties with information security and data integrity ✓ Technical barriers: non-harmonized codification and no longitudinal follow-up of patients across levels of care ✓ Trust issues	✓ Available RWE not centralized ✓ Absence of common indicators' definitions ✓ Variation in data quality/ Trust issues ✓ Lack of continuous patients' data ✓ Lack of experienced scientist to analyse the data ✓	✓ Hurdles to set SIDRA project (aims at generating an integrated information system, provide longitudinal data about care supplied in the health system and outcomes achieved by patients ✓ Information systems across the country are unified ✓ Needs to improve pharma and techno vigilance systems ✓ Lack of resources (professional or financial) to analyse the data	✓ The capacity of decision makers, including government, insurers, and health providers, to analyse all this information is limited ✓ Governmental publications do have the descriptive data but no further analyses

Opportunities	✓ The OS will start monitoring the use of certain high-cost technologies ✓ Extension of the use of EMRs ✓ Data linked to reimbursement and payment is more detailed and of better quality, especially in the private sector	✓ Provides base to generate strategies/studies ✓ Fill-in gaps of data in HTAs ✓ Increases external validity of studies ✓ Unveil aspects of real world care and patterns of all types of healthcare resource use	✓ Use in HTA submissions ✓ Increased use of RWE use in HTAs will promote industry to generate the data	✓ RWE is available from longitudinal data from surveys and registries ✓ Data are freely accessible for any research group interested in further statistical analyses ✓
Key data assets	✓ SUMAR Program: Administrative data on child and maternal healthcare (extending to certain adolescents and adults) ✓ PAMI: Administrative data on medical assistance to the elderly complemented with some disease-specific registries ✓ EMRs in the private sector: Isolated institutions with a well-developed Health Information System could produce outcomes studies linking administrative and clinical data	✓ DATASUS database: collects, processes, and disseminates the healthcare data and information of demographic and healthcare indicators in general, services and products consumed as well as some estimates of mortality and morbidity across specific populations ✓ SIHSUS database: register and reimburse the hospitalisations of patients cared by SUS in public, not-for-profit and for-profit private hospitals contracted by SUS ✓ SIASUS database: reimburse the provision of outpatient healthcare services	✓ Health Inequalities - CASEN survey: a household survey implemented every 2-3 years. Explores explored socioeconomic inequalities ✓ Out-of-pocket expenditure/ house hold surveys (continues data collection): provides information on out of pocket expenditure on health ✓ RWE to examine performance of health system: analysis of healthcare information (hospital, primary care health centres); highly valuable in Chile, but poorly explored	✓ Cancer registries is the basis for official national cancer incidence and prevalence figures ✓ Sivigila registry: high quality multiple disease registry ✓ SISPRO project: patients registry; collects personal information, disease history and resource use; support high cost disease treatment reimbursement; have market share and drug costs
Conclusions	✓ RWE generation and use in its infancy where few existing data assets still face problems with governance, linking and coding.	✓ RWE is generated and used, however, still needs an improvement in data quality. It is progressively used in the decision-making process	✓ RWE has potential to provide health planners the most relevant information to make their decisions. However, it is limited due to scarce resources allocated to fund RWE research, lack of good quality sources of information in all relevant areas and lack of stewardship of the MoH to drive the production of relevant evidence	✓ Health related information has been collected for decades. RWE provide data to HTA (epi data, clinical and economic evaluations). lack of resources to analyse it (mainly universities and consultancies)

6.3 Overview of the Latin American region

In this section we summarize the current situation, opportunities and challenges of the use of RWE in the Latin-American countries under study in order to identify common areas for improvement as well as provide a snapshot of some key data assets available in the region.

Our analysis shows that, while the use of RWE is in its infancy in Latin America, some of the countries use more of RWE, some of them less. Gregory et al. conducted a systematic literature review to define and compare the governance of, and data sources available for, real world research in Latin America (Argentina, Brazil, Central America and the Caribbean (CAC), Chile, Colombia, Ecuador, Mexico, Peru, Venezuela). Administrative and clinical search terms returned over 1800 reports from Latin America, principally from Brazil, Mexico, Argentina and Chile, of which over 700 contained contributory information on data sources for RWE. Of these, 156 addressed international registries or databases including countries in Latin America, 245 reported national registries or databases within one country in Latin America, and 308 reported registries or databases from a single or multiple institutions within a country. Principal administrative categories included claims, prescription and economic data sources (Gregory et al., 2014). Furthermore, there are multiple examples of international collaboration to gather RWE such as the ones presented in Table 9.

Table 9: International examples with data from Latin American countries

Name	Latin-American countries	Data source type	Data holder
GRACE (University of Massachusetts)	Argentina, Brazil, Colombia, Ecuador, El Salvador, Guatemala, Panama, Peru, Uruguay, Venezuela	Global Registry of Acute Coronary Events	Center for Outcomes Research, University of Massachusetts Medical School
ADHERE International (Scios, 2009)	Brazil, Mexico	Acute Decompensated Heart Failure - International Registry	-
PANORAMA (ClinicalTrials.gov, 2013)	Argentina, Bahamas, Brazil, Colombia, Dominican Rep., Ecuador, Mexico, Uruguay, Venezuela	Observational study of patients with pacemakers/cardioverter defibrillators	Medtronic
CESCAS I ((IECS), 2009)	Argentina, Chile, Uruguay	Southern Cone Study of Cardiovascular Disease and Risk Factors detection and follow-up	Instituto de Efectividad Clínica y Sanitaria, Buenos Aires
CCS CDI (Caribbean Cardiac Society, 2011)	Bahamas, Barbados, Belize, Guyana, Jamaica, Martinique, Trinidad-Tobago, US Virgin Islands	Cardiac Diagnostic and Interventional Registry	Caribbean Cardiac Society
CLARIFY (Sorbets et al., 2017)	Argentina, Brazil, Mexico, West Indies	A prospective, observational, longitudinal registry of outpatients with stable coronary artery disease	University of Glasgow, UK
REALISE AF (Hôpital Bichat)	Mexico, Venezuela	Cross-sectional atrial fibrillation registry	Department of Cardiology, Hôpital Bichat, Paris, France
PAHO mortality database (WHO)	43 countries	Pan American mortality database	Pan American Health Organization
RESPONDIA (Reveille, 2013)	Argentina, Brazil, Chile, Costa Rica, Ecuador, Mexico, Peru, Uruguay, Venezuela	Iberoamerican registry of spondyloarthritis	The RESPONDIA group
PLATINO (ALAT)	Brazil, Mexico, Chile, Uruguay, Venezuela	Latin-American Project for Investigation of Pulmonary Obstruction	Latin-American Thoracic Association (ALAT)
BOLD (Imperial College London)	Cuba, Jamaica, Trinidad & Tobago	Survey on the burden of lung disease	Respiratory Epidemiology & Public Health Group at the National Heart & Lung Institute, Imperial College London
AIR (Luisetti, 2013)	Argentina, Brazil	International registry on patients with alpha-1-antitrypsin deficiency	Academia members of the Alpha-1 International Registry
ISAAC (2012)	Argentina, Bolivia, Brazil, Chile, Colombia, Costa Rica, Cuba, Ecuador, El Salvador, Honduras, Mexico, Nicaragua, Panama, Paraguay, Peru, Uruguay, Venezuela	International Study of Allergies and Asthma in Childhood	ISAAC International Data Centre
BIOBADAMERICA (National societies of reumatology, 2008)	Argentina, Brazil, Chile, Colombia, Costa Rica, Dominican Rep., Ecuador, El Salvador, Guatemala, Honduras, Mexico, Paraguay, Peru, Uruguay, Venezuela	National registries on adverse events related to biological therapies in rheumatoid disease	National societies of reumatology

6.4 Discussion

This review of RWE shows that Latin America is a region of diverse healthcare systems, reimbursement structures and regulations. Most countries have the expertise for primary data collection and a framework for secondary RWE collection, however, few have comprehensive national or regional databases and sufficient resources to analyse them. Improvements in the quality of collected data and well-designed prospective population studies are critical to enhance the RWE base. The discussed case studies and their challenges also provide a variety of opportunities to improve the monitoring and evaluation of healthcare services, to ensure that reimbursement strategies are cost-effective, and enable equitable and fair access for all. This is an opportunity to encourage RWE users and data owners to be more proactive in the creating, analysing and communicating data at both regional and national levels.

The focus of research in this white paper has been on various actors in the generation of RWE. Namely, 1) the ministries for health, regulatory agencies, and HTAs interested in RWE enabling evidence-based resource allocation, 2) the pharmaceutical industry that has an inherent interest in gathering RWE for the submission of new drugs and technologies for marketing authorization and reimbursement, 3) patients and their caregivers, with interests in early and affordable access to treatments, co-payment plans for health care and clinical evidence on outcomes of diseases from a real-world setting to enable the best medical management, 4) clinicians and health providers who should be incentivised to collect RWE to improve clinical practice, health outcomes and the standards of care in Latin America, and finally, 5) researchers and experts in the collection and analysis of RWE and the healthcare system as a whole who benefit from better informed policies and decisions.

6.4.1 HTA submission requirements

Our research suggests that the healthcare payer requirements for HTA submissions are one of the key drivers for the generation of RWE in Latin America. The pharmaceutical industry and HTA agencies generate and use RWE throughout the region to support reimbursement of treatments. Chile and Brazil have routine use of both clinical and economic primary data to identify the cost-effectiveness of new treatments when submitting HTAs. In particular, pharmaceutical companies in Brazil, are required to submit HTAs for the reimbursement of high-cost drug (Laranjeira and Petramale, 2013). Meanwhile, the ministry of health is the key driver for the HTA process for high-cost drugs in Chile, which demonstrates that data collection can be triggered by either the regulator or regulated party. Similarly, the Argentinian regulatory framework for the HTA process was formalised in 2017 under the MoH, and it is assumed that RWE analyses methods will be developed to support submissions with the expertise of organisations such as the National Cancer Institute.

6.4.2 Registry data

Secondary data collected in patient registries, population health surveys and surveillance systems are analysed throughout Latin America for the management of health care services. Expert contributions to this white paper reveal that databases in the Chilean and Colombian health systems are amongst the most comprehensive. For instance, the Chilean routine data collection systems for hospital discharges, services provision and resource utilization are widely institutionalised and operate on a national scale, which is a significant improvement on the many Latin American databases that are divided by disease group, provider or region and cannot be synchronised. This study also reveals that the Colombian health system has impressive examples of data collection; registry data is collected by all providers nationwide, including variables such as patient ID, diagnosis, and services used, enabling longitudinal follow-up for research. Unlike registry data in Chile, which is not synchronised with other databases, this Colombian dataset can even be matched to medication sales and is an invaluable input for cost-effectiveness modelling. However, the digitalization of Chilean medical records and improved access to national health statistics gives policy makers a significant advantage for monitoring and evaluating health system planning.

Security concerns and unsynchronised data collection systems can prevent wide dissemination and analysis of registry data. Unlike Chile and Colombia's national registries, Brazilian data is typically isolated to episodes of care, with only rare examples of follow-up data being captured in service-specific databases. As with many national data systems, the confidentiality of patient records is under review in Brazil, and may prevent the dissemination of RWE on a national scale anytime soon. Similarly, national healthcare data in Argentina is limited due to disparate management of services that are divided by region and disease group, with 24 separate provincial institutions managing care within each region (Bello and Becerril-Montekio, 2011, Giovanella et al., 2012). The fragmentation of the Argentinian public sector is further compounded by dominant private health providers, private insurers and a separately managed social security sector. Since high quality data is often collected for HTA or resource allocation purposes in the private sector, Argentinian outcomes may be biased towards wealthier patients. Indeed, a study conducted in Chile concluded that there is a lower rate of mortality in the private sector (Cid et al., 2016), suggesting these outcome inequalities between public and private care may be replicated across Latin America.

6.4.3 Regulation implications

Based on the results of this study, the main implications for the introduction and governance of RWE affect government regulators. There are four principal areas that require a regulation framework to establish a consistent set of guidelines.

First, a central authority ought to steward the interoperability of health information systems with guidelines for the quality, consistency and accuracy of data collected in all provider

settings. As found in the Argentinian case study, without a national regulator to provide universal guidelines for data inputs, healthcare data is inconsistent and cannot be used to produce transferable results. Ideally, regulators should operate at a national level to resolve historical social segmentation in healthcare (Cotlear et al.), and synchronise the data collection inputs for both private and public providers, as well as the different disease groups and corresponding databases.

Second, regulation for the protection of patient privacy is an essential component to building synchronised RWE systems and disseminating findings. Rules such as sharing data only at the aggregate level, or analysing individual data only at a locally stored location are examples of the legal and standard practice frameworks used by European regulators and typical ethical review boards. The practice of sharing individually identifiable data should be carefully monitored and strict rules will need to be put in place to protect the rights of patients, as well as the proper infrastructure to anonymize records and dissociate patients' identity from the data points necessary in each case for each study.

Third, to secure transparency and reproducibility of results, clear regulations are fundamental when releasing data for analysis. An intermediate authority to control and monitor access to patient-level data would help balance the objective of accurate and research results with patient or individual privacy. A clear legal framework that settles issues on data ownership and guardianship would favour all stakeholders achieve transparent models for collaboration and, as such, produce results untainted by suspicion of any kind. This framework would, of course, complement the existing ethics review processes and institutions.

Last, the collection and dissemination of RWE requires resources. IT software, data storage facilities and training for clinical and administrative staff in healthcare facilities are essential for the consistent and transferable collection of data. Regulation and auditing of databases is required to enforce routine data inputs, and importantly, for costs and resource use. Public-private cooperation is required to build consistency among databases across both sectors, and adopt mutually beneficial data collection practices. Close partnership between the sectors may also have further resource generating implications, as private industries such as pharmaceutical or biotechnology companies may invest in the public sector to use national registry evidence, rather than sourcing other international databases. Across Latin America, relatively high proportions of the population are seeking health care in the private sector, and governance of data collection software, practices and administration should include not only public, but private providers as well.

6.4.4 Future research

Research is required to monitor and evaluate the introduction of new digital RWE strategies that have recently been introduced or are in the planning stages across Latin America. For

instance, Chile's newly introduced electronic medical record system, entitled the Information System of the Healthcare Network, and other digitalised records would benefit from auditing to ensure they are capturing a representative sample of patients. In addition, the effectiveness in capturing patient data using digital RWE strategies can be compared against paper record practices for a cost-effectiveness analysis that may inform future practice of other MoHs in the Latin America region.

6.4.5 Conclusion

In conclusion, the ability to capture and analyse RWE has grown exponentially in past years. As follows, the opportunity to improve patient outcomes through evidence-based clinical practice, use of cost-effective treatments and early introduction of new drugs is not to be overlooked. Latin America has in place an established framework of routine data collection strategies, but in many cases, they are fragmented into disease-specific, location-specific and payer-specific organisations. Indeed, Latin American healthcare systems are often characterized by division as a relic of past healthcare inequality; however, unified data collection practices are now being rolled out, and demonstrate promising new sources of national registry data. In the future, Latin Americans can expect to see not only regulation-requirements for RWE, but also evidence-informed outcome data, not from international sources, but from their own population.

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