2022 HTAi Latin American Health Technology Assessment Policy Forum

Real World Evidence: Experiences and challenges for decision-making in Latin America

VII Latin American Health Technology Assessment Policy Forum (Latam Policy Forum). Brasilia, August 2022.

Overview of the Base Document

The document consists of the following sections:

1. **Introduction Section**
2. **Background Section**
3. **Real World Evidence (RWE)** Section
4. **International Experiences Section**
5. **Reference Section**

This document has been drawn up by: Sebastián García Martí - Instituto Efectividad Clínica y Sanitaria (IECS), Guadalupe Montero - Red Argentina Pública de Evaluación de Tecnologías Sanitarias (RedARETS), Verónica Sanguine - Dirección Nacional de Calidad en Servicios de Salud y Regulación Sanitaria - Ministerio de Salud de la Nación Argentina, Federico Augustovski - Instituto Efectividad Clínica y Sanitaria (IECS), and Andrés Pichon Riviere - Instituto Efectividad Clínica y Sanitaria (IECS).

Introduction

In the Glossary of Health Technology Assessment International (HTAi), real-life evidence (RWE) is defined as "evidence derived from the analysis of real-world data" (RWD). RWD is defined as data collected for purposes other than specific research, which provide information on the routine delivery of healthcare and the health status of the target population."[1]

It is then necessary to distinguish between these complementary terms "real-world evidence" (RWE) and "real-world data" (RWD).

RWD refer to data collected outside traditional randomized controlled trials (sometimes called pivotal by regulatory agencies, which data are used as evidence to achieve marketing approval). These RWD consist of a wide range of possible information on the various health conditions people may have and on the provision of health care, from a wide variety of sources, such as administrative databases, digital medical records, billing data, product records, records of specific diseases, data generated by patients, as well as data from mobile device applications among others.

RWE is instead the evidence obtained from the analysis of the RWD on the use, risks, and benefits health technologies entail, as well as the health status of a population.

Some of the potential uses of "real life" studies at different stages of the health technology assessment cycle are the characterization of those patients or diseases with unmet or poorly controlled needs, the identification of not so frequent adverse effects by pharmacovigilance, or the description of the usual treatment patterns with their consequent usefulness to define standard comparators in a clinical trial or in an economic evaluation. They also provide information for entering risk-sharing agreements or the monitoring of interventions once these are incorporated. Sometimes this type of information can complement randomized controlled clinical trials to

[1] Oortwijn W: Real-world evidence in the context of health technology assessment processes- from theory to action. HTAi Global Policy Forum. Dec 2018. Available in: https://htai.org/wp-content/uploads/2019/02/HTAiGlobalPolicyForum2019_BackgroundPaper.pdf

evaluate the comparative effectiveness of different technologies or interventions in certain scenarios where their execution may be more complex or difficult.[2]

RWD and RWE are becoming increasingly important at different stages of the health technology life cycle, from the initial 'regulatory' stages to those of adoption and coverage by health systems, also including their monitoring once they are actually incorporated.[3]

The objective of the seventh 2022 Latin American Health Technology Assessment Policy Forum will be to discuss and understand the usefulness and potential uses of RWE in HTA processes and decision-making, analyze the problems that HTA agencies and different stakeholders face regarding its use, and define a series of key principles and actions that can serve to guide the establishment and development of the use of RWE in health technology assessment and decision-making in Latin America.

What is Health Technology Assessment (HTA)?

HTA is a multidisciplinary process that uses explicit methodologies to determine the value of a health technology throughout its lifecycle (O'Rourke 2020). Its purpose is to inform the decision-making process to promote equitable, efficient, and high-quality health systems. This information is used by health systems to make decisions that primarily affect the way health resources are allocated, such as the decision to cover a certain health technology, or the decision to incorporate it into a benefits package.

Health technologies have become an indispensable part of any health system and their use has increased in recent decades. The introduction of new technologies has generally involved significant benefits, in terms of prevention, safety, improvements in health and quality of life, or reduction of adverse effects. However, in a context in which resources are limited, the correct incorporation and dissemination of technologies has become a challenge, and in some cases, a serious problem.

The rapid emergence of technologies and the increasing volume of available evidence have now become a reality for all health systems. Providing health services involves making decisions about which interventions should be offered (and implicitly or explicitly, which ones should not), how the health system is to be organized, who will pay for these interventions; as well as how and who should provide them. The challenge is to achieve adequate health outcomes with the available resources, once the social values, expectations, and demands of the population have been duly contemplated.

Currently, a large number of countries have committed to achieving universal health coverage (UHC) for their population, this being one of the objectives prioritized by the World Health

[2] Anneman, L. The use of real world data throughout an innovative medicine's lifecycle. Disponible in: https://www.riziv.fgov.be/nl/themas/kost-terugbetaling/door-ziekenfonds/geneesmiddel-gezondheidsproduct/terugbetalen/innovatieve-geneesmiddelen/Paginas/innovative- medicins-lifecycle.aspx

[3] McNair D, Lumpkin M, Kern S, Hartman D. Use of RWE to Inform Regulatory, Public Health Policy, and Intervention Priorities for the Developing World. Clin Pharmacol Ther. 2022 Jan;111(1):44-51

Organization (WHO). In the context of the UHC, the prioritization of interventions is a central strategy, and in the documents developed by this body it is considered of the utmost importance that it be carried out based on the best available evidence and through a deliberative process that takes social values into account[4][5] . Within this context, health decision-makers have come to need more and more reliable and detailed information to help them make transparent and legitimate decisions when setting priorities, in order to obtain the maximum benefit on limited budgets. The growth and development of HTA reflects this demand for solid and transparent information that serves as a guarantee to make decisions on the development, incorporation, and dissemination of health technologies[6]. HTA has precisely arisen from this growing concern about the expansion of new and expensive health technologies in the 1970s and the limitations of health systems to finance their use. As a discipline it has evolved since the 70's to become a multidisciplinary specialty whose purpose is to gather and summarize the available evidence to help health decision-makers, health professionals, and patients understand the relative value of technologies.

The development of HTA has been particularly remarkable over the past 20 years and is today an essential component of health systems in many countries. Several initiatives have emerged in the Latin American and Caribbean (LA) region. Argentina, Brazil, Colombia, Chile, Mexico, and Uruguay have HTA agencies that are members of INAHTA (acronym for International Network of HTA Agencies), and several Latin American countries currently apply HTA, to various extents, to decision-making on resource allocation. Most of these initiatives in the region are grouped under RedETSA, the Latin American Health Technology Assessment Network (http://redetsa.org/), coordinated by the Pan American Health Organization (PAHO).

HTA is potentially an extremely useful tool for decision makers. However, if not executed and used properly, there is a risk of producing an inefficient allocation of resources, covering interventions of little or no benefit, preventing or delaying patient access to useful health technologies, exposing patients to unnecessary risks, and sending the wrong messages to technology producers, among others[7]. In turn, HTA is not a purely technical practice, and the decision-making process must contemplate increasingly broader dimensions. For these reasons, since the decisions to be made through the HTA process have the potential to affect a great number of individuals and institutions, a set of basic principles has been proposed for HTA to abide by. These principles include aspects such as transparency in the process of carrying out an HTA and decision-making, the involvement of relevant stakeholders, the existence of explicit

[4] Terwindt Hotels F, Rajan D, Soucat A. Priority-setting for national health policies, strategies and plans. In: Schmets G, Rajan D, Kadandale S, eds. Strategizing national health in the 21st century: a handbook: World Health Organization (WHO); 2015:71

[5] World Health Organization (WHO). Making fair choices on the path to universal health coverage. Final report of the WHO Consultative Group on Equity and Universal Health Coverage 2014: http://apps.who.int/iris/bitstream/10665/112671/1/9789241507158_eng.pdf?ua=1. Accessed 11- 3-2016

[6] Gabbay J, Walley T. Introducing new health interventions. BMJ. 2006;332(7533):64-65.

[7] Wilsdon T, Serota A. A comparative analysis of the role and impact of health technology assessment. . London:UK: Charles River Associates; 2011: http://www.phrma.org/sites/default/files/pdf/hta_final_comparison_report_13_may_2011_stc1.pdf

mechanisms to decide which technologies are to be evaluated, and the existence of a clear link between assessment and decision making. [8][9][10] Many of these aspects were addressed in previous editions of the Latin American HTAi Policy Forum.[11][12][13][14][15]

Background and Objectives of the Forum

The Health Technology Assessment Policy Forum is an activity organized by HTAi (Health Technology Assessment International). It was created in 2004 with the aim of providing a neutral space to carry out strategic discussions on the present state of HTA, its development, and its implications for health systems, the industry, patients, and other stakeholders. It convenes representatives of three main groups of institutions: 1) decision-makers on matters of coverage and reimbursement/prices of medicines and devices in health systems; (2) agencies carrying out HTA in support of these decisions; and 3) technology-producing biomedical companies. It has been carried out for 17 years with a focus on Europe and the USA and for 10 years in Asia. In 2016 it was also held in Latin America for the first time, the present Forum being the seventh meeting to be held in the region.

The approach, agenda, and logistical details were developed by an Organizing Committee composed of the President of the Forum and representatives of the participating institutions (three representatives of the public sphere and three representatives of the field of technology producing companies). The Institute for Clinical Effectiveness and Health Policy of Argentina (IECS – www.iecs.org.ar) acted as the Scientific Secretariat.

---

[8] Daniels N, Sabin J. Setting limits fairly: learning to share resources for health. 2nd ed. New York: Oxford University Press; 2008

[9] Drummond MF, Schwartz JS, Jönsson B, Luce BR, Neumann PJ, Siebert U, Sullivan SD. Key principles for the improved conduct of health technology assessments for resource allocation decisions. Int J Technol Assess Health Care. 2008. Summer;24(3):244-58; discussion 362-8

[10] Pichon-Riviere A, Augustovski F, Rubinstein A, Martí SG, Sullivan SD, Drummond MF. Health technology assessment for resource allocation decisions: Are key principles relevant for Latin America? Int J Technol Assess Health Care. 2010 Oct;26(4):421-7

[11] Pichon-Riviere A, Soto NC, Augustovski FA, García Martí S, Sampietro-Colom L. Health techonolgy assessment for decision making in Latin America: good practice principles. Int J Technol Assess Health Care, 34:3 (2018), 1-7

[12] Pichon-Riviere A, Soto NC, Augustovski FA, Sampietro-Colom L. Stakeholder involvement in health technology assessment process in Latin America. Int J Technol Assess Health Care, 34:3 (2018), 1-6

[13] Pichon-Riviere A, GarciaMarti S, Oortwijn In Augustovski F, SampietroColom L (2019). Defining the Value of Health Technologies in Latin America: Developments in Value Frameworks to Inform the Allocation of Healthcare Resources. International Journal of Technology Assessment in Health Care 35, 64–68

[14] Pichon-Riviere A, Augustovski F, García Martí S, Alfie V, Sampietro-Colom L (2020). The link between health technology assessment and decision making for the allocation of health resources in Latin America. International Journal of Technology Assessment in Health Care 36, 173–178

[15] Pichon-Riviere A, Augustovski F, García Martí S, Alcaraz A, Alfie V, Sampietro-Colom L (2021). Identification and selection of health technologies for assessment by agencies in support of reimbursement decisions in Latin America. International Journal of Technology Assessment in Health Care 1–8

The process of selecting the topic for this seventh Forum began during the sixth Forum and included the following steps:

1. A list of potentially relevant topics based on the proposals/topics suggested by the members of the Latin American Forum was drawn up and a vote was held during the closing of the 2021 Forum to identify the most urgent topics for 2023.
2. This list was sent to the members of the Organizing Committee for their comments/suggestions.
3. The final topic was selected through a deliberative process within the Organizing Committee

Based on this process, the topic selected for this seventh forum is "Real World Evidence: Experiences and challenges for decision-making in Latin America".
This seventh edition of the Latin American Policy Forum is concatenated with the previous six:
2016 Policy Forum: The first LA Policy Forum was held in Costa Rica. At this meeting the "Principles of good practices in the application of Health Technology Assessment in decision-making in Latin America" were discussed. As a result of this forum, the principles deemed as most relevant to promote the application of HTA in LA were:
• Transparency in the processes of carrying out HTA and communicating its results
• Involvement of relevant stakeholders in the HTA process
• Existence of appeal mechanisms
• Existence of clear mechanisms for the establishment of priorities in HTA
• Existence of a clear link between assessment and decision-making
2017 Policy Forum: This second Policy Forum, held in Lima, had as its central theme the incorporation of different stakeholders into the Health Technology Assessment process, an aspect that had been identified as a priority during the first Policy Forum.
2018 Policy Forum: It was held in Montevideo in 2018 and it considered value frameworks in HTA.
2019 Policy Forum: It was held in Buenos Aires, and it was focused on the relationship between HTA and decision-making.
2020 Policy Forum: It was held online, and the discussion covered the mechanisms used by HTA agencies to prioritize the assessments to be carried out.
2021 Policy Forum: Also held online, the debate in this case was about the role of deliberative processes in HTA
(All the results of the discussions held during these five Latin American Policy Forums are available in a series of publications: Pichon-Riviere et al 2018-2021)

The main objectives of this seventh Health Technology Assessment Policy Forum in Latin America will be:

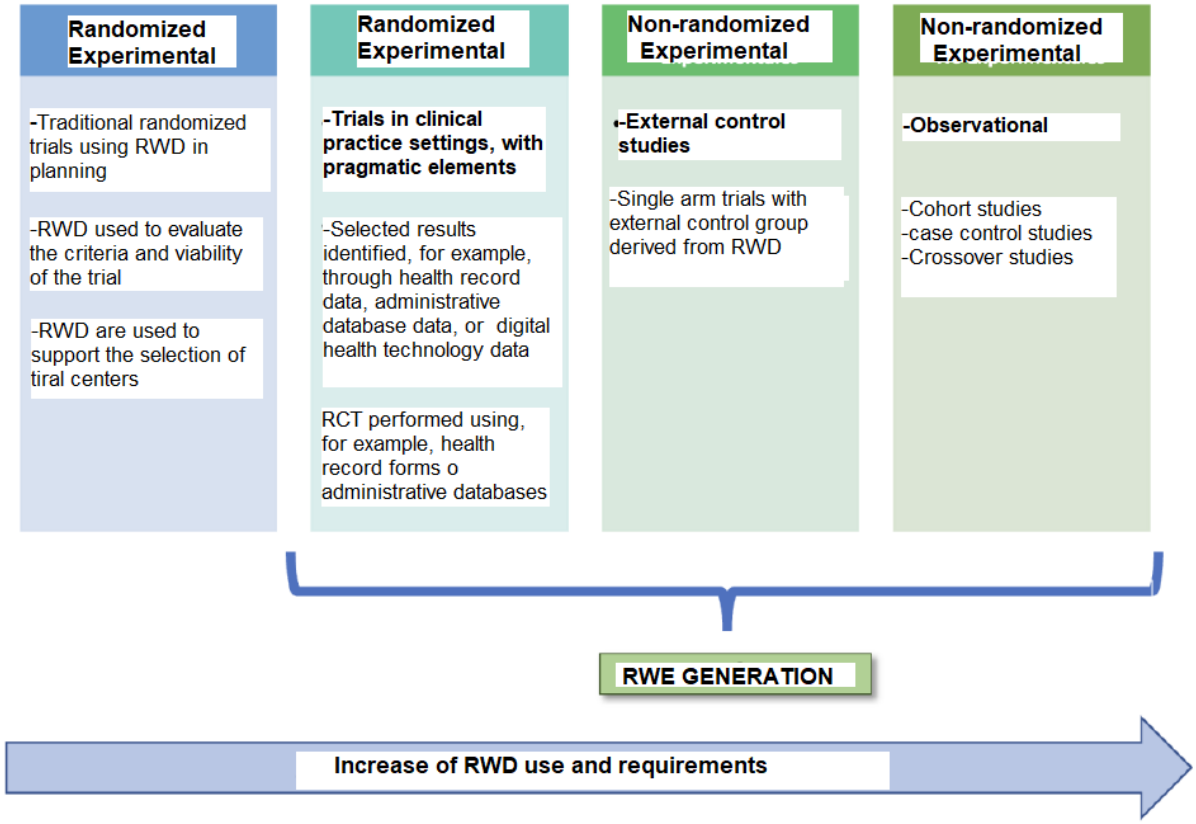
- Explore the current state of the use of RWD/RWE in the different stages of HTA processes in Latin America (also including aspects related to the generation and analysis of RWD)
- Explore the positive/negative aspects, advantages/disadvantages, and main consequences/difficulties that using RWE entails in the Region

- Explore the limitations/barriers/risks, as well as the opportunities/facilitators for the implementation/expansion of the use of RWE in the Region
- Discuss and identify the main contextual aspects that should be taken into account in the region when implementing/expanding the use of RWE, as well as the principles of good practice and requirements that a health system should meet to carry them forward
- Discuss the potential applicability of the different models used abroad to health systems in Latin America and generate a set of recommendations to guide the establishment and development of the use of the RWE in health technology assessment and decision making in Latin America.

Introduction to RWE. Definition. Background. Conceptual framework

As mentioned in the introduction, RWE is considered to be meticulously analyzed information arising from the analysis of RWD (data collected without having a research study as a specific purpose).

The figure below describes both the different designs and data types and their potential usefulness in the context of RWE generation.



Increasing RWD use and requirements in different types of RWE study designs
Graph adapted from Concato J. Real-World Evidence - Where Are We Now? N Engl J Med. 2022 May 5;386(18):1680-1682.

RWD and its analysis and transformation into RWE, are currently used to a greater or lesser extent by the different stakeholders within a health system. It can be applied to procedures such as the ones listed below[16]:

- Characterize health conditions, interventions, care pathways, and patient outcomes and experiences.
- Understand the safety of medical technologies, such as medications, devices, and interventional procedures

[16] Real-world evidence framework. NICE UK. https://www.nice.org.uk/about/what-we-do/real-world-evidence-framework-feedback

- Assess the impact of interventions (including diagnostic tests) on service delivery and care decisions
- Evaluate the applicability of clinical trials to patients under usual practice conditions
- Design, complete, and validate economic models (including estimates of the use of resources, quality of life, event rates, prevalence, incidence, and long-term outcomes)
- Develop or validate digital health technologies
- Identify, characterize, and address health inequalities
- Provide information for the generation of risk-sharing agreements

A specific aim of both regulatory agencies and health technology assessment agencies is to supplement information from randomized controlled clinical trials (RCTs) on occasion, when their performance may be complex or difficult to carry out in the assessment of comparative effectiveness between interventions.

Randomized clinical trials (RCTs) are the priority source when analyzing evidence on the efficacy of interventions. Randomization ensures that any difference in the initial characteristics across groups to be compared is evenly distributed among them.

However, RCTs are sometimes unavailable or not directly relevant to decisions about patient care. Although RCTs often manage to inform on the efficacy of new health technologies –which in fact is a requirement set by regulatory agencies authorizing their commercialization (FDA, EMA, ANVISA, etc.)- they rarely manage to answer the question of health systems (payers, providers) on the effectiveness of technologies under the usual conditions.

In turn, RCTs can be particularly difficult to perform in populations with rare diseases due to the small number of patients, unmet needs that make it difficult to conduct studies in these populations, or variations in clinical practice.

In some cases, it is not possible to obtain information from RCTs, for a number of reasons, including[17]:

> – randomization is considered unethical or unfeasible (e.g., for some rare or serious diseases with significant unmet needs)
>
> – technical challenges make randomization impractical, which is more common for medical devices and interventional procedures
>
> – there is no funding available for a trial (e.g., where the intervention is already used in standard practice).

Similarly, high-quality RCTs can be a challenge for medical devices and interventional procedures due to the difficulty in blinding, the importance of learning effects, changes in the standard of care

[17] Real-world evidence framework. NICE UK. https://www.nice.org.uk/about/what-we-do/real-world-evidence-framework-feedback

that make it difficult to choose comparators, changes in the characteristics of a technology over time that can impact their performance, and limited research capability or access to funding.[18]

It may also happen that the evidence from RCTs is not sufficient for decision-making when the comparator does not reflect the care standard, relevant population groups are excluded, there are important differences in patient behavior, care pathways or settings differ from implementation in usual practice, follow-up time is limited, non-validated substitute results are used, or the quality of trials is poor.[19]

It is in these contexts that some other designs included in what is considered RWE can be used. Among these are observational studies such as prospective or retrospective cohorts, or other designs such as "pragmatic" clinical trials.

On the other hand, apart from the fact that RWE could be used to complement information from other types of studies and accelerate access to technologies by some patient groups, there are deterrents to its use, including, among others:[20]

– Challenges to access high-quality data in a timely manner

– Concerns about the source and quality of the data

– Risk of bias due to information limitations

– Limited confidence in the integrity of some real-world evidence studies due to the complexity of the generation of evidence and the opportunity to "select" results

- Difficulties in its analysis that limit its internal validity

[18] Fleurence RL, Shuren J. Advances in the Use of Real-World Evidence for Medical Devices: An Update From the National Evaluation System for Health Technology. Clin Pharmacol Ther. 2019 Jul;106(1):30-33

[19] Real-world evidence framework. NICE UK. https://www.nice.org.uk/about/what-we-do/real-world-evidence-framework-feedback

[20] Framework for FDA's Real-World Evidence Program. FDA. 2018

Role and potential utility of RWE throughout the lifecycle of HTA

RWE can have different uses during the different phases of a health technology lifecycle, i.e., the development phase, the market access phase, the usage phase once incorporated, and even obsolescence.

In each of these phases, different designs or data sources are used. In this document, when referring to RWE, we assume that it is generated from RWD, the necessary input to produce this type of information.

The background paper of the 2018 Global Policy Forum[21], on RWE and HTA, discusses the role and potential usefulness of RWE throughout the HTA lifecycle. A number of potential applications were identified at the different stages of the lifecycle as mentioned below (mainly based on a paper from Annemans 2017).[22]

During the development phase

During the development phase some of the uses of RWE can be to better characterize diseases, patient populations, and understand current needs, as well as to allow the execution of disease burden studies; identify those patients who are eligible to participate in research studies, thus facilitating recruitment processes; enable the performance of "pragmatic or realistic" clinical trials, thus allowing to incorporate results of the usual clinical practice.

During the market access phase

Marketing approval (regulatory agencies):
RWE can provide additional information for the approval of technologies, especially in scenarios where evidence from RCTs is not available, as they are innovative technologies, they involve rare or ultra-rare diseases, or where it is ethically impracticable to conduct an RCT, for example. RWE can also provide additional backup information with greater external validity than RCTs, and offer data inherent to different population subgroups, to the use outside the initially approved indications (the so called "off-label" use), to the inappropriate use of technologies, and to validate the use of surrogate endpoints in certain pathologies.[23]

---

[21] Oortwijn W: Real-world evidence in the context of health technology assessment processes- from theory to action. HTAi Global Policy Forum. Dec 2018. Available in: https://htai.org/wp-content/uploads/2019/02/HTAiGlobalPolicyForum2019_BackgroundPaper.pdf

[22] Anneman, L. The use of real world data throughout an innovative medicine's lifecycle. Available in: https://www.riziv.fgov.be/nl/themas/kost-terugbetaling/door-ziekenfonds/geneesmiddel-gezondheidsproduct/terugbetalen/innovatieve-geneesmiddelen/Paginas/innovative- medicins-lifecycle.aspx

[23] Use of real-world evidence in single-drug assessments. Ottawa: CADTH; 2018. (Environmental scan; no. 74)

RWE can also contribute to a better understanding of patients' usual treatment and standards of care, as well as a better understanding of complications, adverse events, disease progression, use of resources, and costs, which can potentially be used to conduct Economic Evaluations.

For coverage decisions (health system payers, HTA agencies, providers):

Sometimes, besides the contribution of complementary information to the RCTs when deciding on coverage policies, RWE can be useful for the generation of risk-sharing agreements or conditional coverage with the development of evidence that sometimes allows to optimize decisions in scenarios of uncertainty about the true benefit of the technologies.

During the usage phase, after their incorporation

During this phase, RWE can allow to evaluate the results of the technologies in real practice (adherence, identification of subgroups of patients deriving the greatest benefits, or safety evaluation). This information can serve as an input into outcome-based risk arrangements, the reassessment of the true benefit of a technology that could lead to evaluating its divestment, or as an input for the development of clinical decision support systems.[24]

Challenges of RWE in the context of HTA

Increased use of RWE requires adequate and quality data sources (RWD) (e.g., digital health records, administrative databases, patient records, wearable devices, social media platforms, patient organization websites, genomics, biomarkers). On the other hand, there is an ever-increasing production of data from "wearables", which poses challenges when it comes to using such data not only in terms of their analysis but in terms of privacy and access thereto.

As described in the Duke-Margolis Center for Health Policy 'white paper' [25] it is a known fact that data and evidence are not the same; RWD are necessary but not sufficient to generate RWE. There is a clear need to keep these concepts separate.

Currently under discussion are aspects such as the appropriate time and manner in which RWE is incorporated into an HTA. Also, on the impact its incorporation would have for different stakeholders, such as patients, health professionals, payers, manufacturers, decision-makers, and technology assessors.

[24] Pearson SD, Dreitlein WB, Towse, A, Hampson G, Henshall C. A framework to guide the optimal development and use of real-world evidence for drug coverage and formulary decisions. J Comp Eff Res. 2018;7:1145–52

[25] Characterizing RWD Quality and Relevancy for Regulatory Purposes. October 2018. Duke-Margolis Center for Health Policy

During the Global Policy Forum on RWE held in 2018 the key challenges related to the use of RWE identified by HTAi[26] and applicable to the region were:

• For which HTA questions could RWE be accepted as fit for the purpose?
• When throughout the technology lifecycle is RWE to be used?
• Quality of data from real-world sources
• Data infrastructure and data accessibility
• Transferability issues

- For which HTA questions would using RWE be acceptable or useful

Some key questions related to this topic include: In what cases can HTA benefit from the use of RWE? And in turn, to what extent do decision-makers and payers accept RWE?

RWE can be used for multiple purposes. Some of those purposes include providing evidence on the natural history and epidemiology of a disease, providing information on treatment and interventions in routine practice, informing regulatory approval decisions, and its application to monitoring the use of technologies once these are incorporated; on the other hand, and increasingly so in HTA, especially in cost-effectiveness analysis, payers' coverage decisions or payment agreements are based on results. RWE can also be useful for estimating healthcare costs as well as providing information to supplement evidence from RCTs or other existing research findings.

Beyond these listed potential utilities, there is some resistance from various stakeholders to use RWE and to understand its usefulness, as detailed in the background paper of the Global Policy Forum, due to lack of understanding, access to data sources, or collaboration between the different stakeholders, which problems are common to different regions.[27]

- When to use RWE in the lifecycle of technologies

There is no clear consensus among the various stakeholders on when to use RWE. However, some stakeholders believe that RWE does have the potential to rationalize the use of health technologies and drive divestment decisions.

[26] Oortwijn W: Real-world evidence in the context of health technology assessment processes- from theory to action. HTAi Global Policy Forum. Dec 2018. Available in: https://htai.org/wp-content/uploads/2019/02/HTAiGlobalPolicyForum2019_BackgroundPaper.pdf

[27] HTAi Policy Forum Series Newsletter. Universal health care in the Asia Region: overcoming the barriers using HTA and Real World Data. December 2017. Available at: https://htai.org/wp-content/uploads/2018/05/HTAi_Asia-Policy-Forum_newsletter_20171208b.pdf

Regulatory agencies such as the U.S. FDA and the EMA in the European Union, or Health Canada, use RWE to supplement data from RCTs, both during and after pre-marketing authorization for monitoring and supervision of technologies.[28]

In addition to these uses, EMA has identified some potential barriers to the use of RWE including poor data quality and limited access to data sources, unsuitable definition of outcomes, and extrapolation of data from non-European registries.[29]

- Quality of data from real-world sources

Another aspect mentioned in the background paper of the Global Policy Forum that is very relevant to our region relates to data quality.

Incomplete data, heterogeneity between different sources and the difficulty to link them, as well as certain difficulties in analyzing data not collected for specific research purposes, are key issues that need to be addressed in the context of RWE.[30]

Another challenge is to identify robust methodologies for collecting and analyzing RWD (standardization) to estimate efficacy and effectiveness. [31] This is partly due to differences in clinical practice among different countries or regions, leading to a great heterogeneity in RWD. This situation compromises the use of RWD and RWE. In this regard, it is necessary to define minimum sets of data across the different sources to subsequently allow the interoperability and extrapolation of the same. There are also some initiatives such as DARWIN in the European Union to promote the standardization of RWD and facilitate their subsequent use, as well as increase their potential usefulness.[32]

Another aspect related to data quality concerns the transparency of the RWE generated from RWD. The ISPOR-ISPE special task force published a paper[33] that addresses several key aspects of transparency in the overall planning of the study as well as in its execution to facilitate replicability. Specific recommendations are provided for studies that include data on treatment efficacy with previously specified hypotheses (so-called 'HETE' studies, Hypothesis Studies

---

[28] Use of real-world evidence in single-drug assessments. Ottawa: CADTH; 2018. (Environmental scan; no. 74)

[29] Plueschke, K., McGettigan, P., Pacurariu, A., et al. EU-funded initiatives for real world evidence: descriptive analysis of their characteristics and relevance for regulatory decision-making. BMJ Open 2018; 8 (6): e021864

[30] Considerations for the Use of Real-World Data and Real- World Evidence to Support Regulatory Decision-Making for Drug and Biological Products. Draft Guidance. FDA December 2021

[31] Anneman, L. The use of real world data throughout an innovative medicine's lifecycle. Available in: https://www.riziv.fgov.be/nl/themas/kost-terugbetaling/door-ziekenfonds/geneesmiddel-gezondheidsproduct/terugbetalen/innovatieve-geneesmiddelen/Paginas/innovative- medicins-lifecycle.aspx

[32] Data Analysis and Real World Interrogation Network (DARWIN EU®) https://www.ema.europa.eu/en/about-us/how-we-work/big-data/data-analysis-real-world-interrogation-network-darwin-eu

[33] Orsini LS, Berger M, Crown W, Daniel G, Eichler HG, Goettsch W, Graff J, Guerino J, Jonsson P, Lederer NM, Monz B, Mullins CD, Schneeweiss S, Brunt DV, Wang SV, Willke RJ. Improving Transparency to Build Trust in Real-World Secondary Data Studies for Hypothesis Testing-Why, What, and How: Recommendations and a Road Map from the Real-World Evidence Transparency Initiative. Value Health. 2020 Sep;23(9):1128-1136.

Evaluating Treatment Effectiveness) for the protocol [34]to be recorded and its design before it is actually carried out, as well as the publication of the results or deviations from the protocol, and also the analysis, which allows to increase transparency and include the different stakeholders (HTA agencies, payers, regulatory agencies, doctors, patients, or industry) in the design, execution, and dissemination of these studies.

- Infrastructure and data access

Differences in the content and structure of diverse databases that could be used can lead to significant challenges in sharing RWD both within a country and between countries and/or regions. There are also considerable challenges regarding the lack of governance of these. Sometimes there are no regulations for collaboration, there are no incentives for data sharing, problems or aspects related to patient consent and data privacy and security can hinder access and lead to high data protection costs to comply with local regulations. As mentioned above, the European Union is making progress in these aspects that promote the use of RWD through the DARWIN initiative.

Another aspect to keep in mind is that improving the infrastructure to generate RWD can be expensive and complex, as it may require changes in usual practice, including the creation of support infrastructures, such as computer systems.

- Transferability

Data collection, especially RWD, is often related to specific contexts (e.g., a local health system), particular care or patient characteristics, or even the level of knowledge or variations in clinical practice.

For example, incorporating usual care as a comparator in a study (dose frequency, route of administration, monitoring) may differ between different settings and populations. These usual differences become more evident as the RWD get more specific to distinct contexts, thus raising definite aspects about transferability of the results.

Status and recommendations regarding global RWE utilization processes

[34] Real-World Evidence Registry
https://www.ispor.org/strategic-initiatives/real-world-evidence/real-world-evidence-registry

Various agencies, both in the regulatory field and in HTA in general, incorporate RWE into their evaluation processes. However, the extent of use is heterogeneous, although certain common aspects can be pointed out.

The Canadian health technology assessment agency -CADTH – has conducted a survey on the use of RWE by different HTA agencies in the world, in which the following studies are mentioned.[35]

Makady et al.[36] examined RWE use policies in 6 HTA agencies in European countries (NICE, TLV, IQWiG, HAS, ZIN and AIFA), overall, the 6 agencies consider RWE studies to be of a lower quality of evidence than RCTs.
They believe that the special circumstances in which the use of RWE could be contemplated are absence of RCTs (NICE, ZIN, IQWiG), as in the absence of direct comparison RCTs RWE can be used to report the effectiveness of indirect comparisons (NICE, ZIN) or to supplement data from RCTs in specific subgroups not covered by RCTs, or for longer-term results (NICE, ZIN). In all cases, these agencies request that the need to use RWE be adequately explained and the potential biases and their consequences on the estimation of the effect of the technologies under evaluation be specified.

In the report conducted by CADTH the use of RWE by the agencies in Canada, Australia, and New Zealand was evaluated, with similar results to those found in Makady's report. Notwithstanding the fact that the agencies consider that RWE studies entail a higher risk of bias than RCTs, they acknowledge their particular value in the following situations: conditions that can be fatal in the short term without an intervention ("dramatic effect"), an unmet need of the highest magnitude, difficulty in performing RCTs due to very low number of patients or because they are considered unethical (e.g., women during pregnancy), and to identify rare or long-term serious adverse effects. Where RCTs do exist, RWE studies can provide information about treatment adherence, the persistence of its effects, or its dose, as well as the use of technologies in routine practice.

Another cited report by Griffiths[37] assessed the proportion of use of RWE in the NICE, IQWiG, and CADTH health technology assessment reports, which was 38%, 12%, and 13% respectively, with RWE being the only evidence presented at 4%, 4%, and 6%, respectively.

In general, the use of RWE as the only source for assessing the advantages of interventions is uncommon and when it is indeed used it requires a careful approach.

---

[35] Use of real-world evidence in single-drug assessments. Ottawa: CADTH; 2018. (Environmental scan; no. 74)

[36] Makady A, Ham RT, de Boer A, Hillege H, Klungel O, Goettsch W, et al. Policies for use of real-world data in health technology assessment (HTA): a comparative study of six HTA agencies. Value Health. 2017 Apr;20(4):520-32.

[37] Griffiths EA, Macaulay R, Vadlamudi NK, Uddin J, Samuels ER. The Role of Noncomparative Evidence in Health Technology Assessment Decisions. Value Health. 2017 Dec;20(10):1245-51

The use of RWE is being explored more actively in the preliminary phases of market entry decisions, in the extension of indications, or in those situations where the magnitude of unmet needs is high, or in post-incorporation surveillance in use.

Specific aspects about the use of RWE in HTA in Latin America

In Latin American countries, in recent decades there has been an increase in the number of agencies and organizations performing HTA, as well as a growing interest in expanding the sources of information within health systems beyond controlled clinical trials, by academic organizations, evaluators, payers, and producers.

However, the availability of adequate sources of RWD is very scarce, and there are deficiencies in relation to the reliability and completeness of the data. For this reason, the reluctance of the assessment agencies to incorporate this type of sources into the HTA is still significant.

At the regional level, a review conducted by Justo et al. in 2019[38], which included a literature review and consultations with key opinion leaders from Argentina, Brazil, Chile, and Colombia, described the main use at the time as that of pharmacovigilance and technovigilance.

Regarding coverage decisions, although no formal processes have been identified, assessment agencies generally incorporate evidence from observational data, especially into budget impact analyses or economic evaluations.

The greatest progress in its use is described in Brazil, although in relatively small populations and with little development of interoperability between databases and record systems. In the other countries included in this review, more and more economic evaluations are being carried out for decision-making, but the use of RWE tends to be especially promoted by health technology producers, though it does not constitute a formal part of market access agreements in conjunction with assessment agencies, decision makers and/or payers.

Also mentioned in this review is the existence of government records of specific diseases that can be useful data sources in the generation of RWE.

Similar to the challenges and limitations found in other regions, the review mentions the uncertainty about the quality or integrity of the databases, or the quality and security of the same as impediments. It also mentions a lack of skilled personnel specifically trained for data analysis and methodological management, and the scarce dissemination of good practices in the process of generating RWE based on the available RWD. It also mentions a lack of confidence between the different stakeholders as there are no integrated or trust-based actions, which adds to the difficulty of using RWD and RWE.

[38] Justo N, Espinoza MA, Rat B, Nicholson M, Rosselli D, Ovcinnikova O, García Martí S, Ferraz MB, Langsam M, Drummond MF. Real-World Evidence in Healthcare Decision Making: Global Trends and Case Studies From Latin America. Value Health. 2019 Jun;22(6):739-749

International Experiences Section

Two HTA assessment agencies (NICE and CADTH) and one regulatory agency (FDA) were then selected to describe their RWE utilization processes and frameworks. The processes of using these are described.

NICE RWE Usage Framework (United Kingdom)[39]

In its framework document for the proper use of real-world data NICE provides detailed guidance and clearly describes the best practices for planning, conducting, and reporting RWE studies to enhance the quality and transparency of evidence. This document points out the elements to be considered at the different stages of evidence generation:

1. When planning:

- Clearly define the research question, the population eligibility criteria, interventions, outcomes, and target population.
- Plan the study prospectively and make the protocols public.
- Choose data from good sources and of sufficient quality and relevance to address the research question
- Justify the need for increased primary data collection, weighing the burden on patients and healthcare professionals against the value of additional data
- Use the data in compliance with the local law, local government processes, codes of practice, and data owner requirements

2. During execution:

- Use study designs and statistical methods that are appropriate to the research question, considering the main risks of bias
- Use sensitivity and/or bias analyses to assess the robustness of studies against risks of bias or data analyses.
- Ensure quality to guarantee the integrity and quality of the study.

[39] Real-world evidence framework. NICE UK
https://www.nice.org.uk/about/what-we-do/real-world-evidence-framework-feedback

3. Report generation:

- Disclose the study design and analytical methods in sufficient detail to allow independent researchers to fully understand what was done and why, so they can critically evaluate the study, and reproduce it.
- Reports should also describe: the source, quality, and relevance of the data, data safeguarding, patient follow-up from initial data to final analysis, patient characteristics (including missing data) and follow-up details in general, and among key population groups, the results of all planned and performed analyses (clearly indicating any analyses that had not been previously planned), risk of bias assessment and extendibility to the target population.

CADTH RWE Usage Framework (Canada)[40]

Generally speaking, various aspects common to the use of data in general are mentioned in CADTH's framework of use of RWE. Those differential aspects are focused on the evaluation of the quality and collection of the data to be used.

They specifically define that data sources and their coding systems if any (CIE, ATC for example) and all the forms of relationship between the different bases that allow their joint analysis must be described in detail.

When using administrative databases, it is mentioned that it is a good practice to perform some validation method that allows to evaluate the representativeness of the data with respect to the population of interest.

On the other hand, it is also mentioned that access to the different data sources used must be provided.

The analysis approach should be clearly described, as should treatment of incomplete or absent data.

United States (FDA) RWE Utilization Framework[41]

[40] Elements of Real World Data/Evidence Quality throughout the Prescription Drug Product Life Cycle https://www.canada.ca/en/services/health/publications/drugs-health-products/real-world-data-evidence-drug-lifecycle-report.html

[41] Framework for FDA Real World Evidence Program. Dec 2018 https://www.fda.gov/media/120060/download

The Food and Drugs Administration (FDA) created a framework to evaluate the potential use of RWE in the approval instance of new technologies in 2018, in the context of a specific program for the use of RWE in approval decisions.

There is a long history of using RWE in the context of safety assessment and post-marketing monitoring. In limited circumstances, the FDA has accepted RWE for product approval, especially in the context of oncological or rare diseases.

This program focuses on the evaluation of the effectiveness of new technologies through RWE, on the aspects of modifications and / or extensions to the indications of products already approved, changes in dosages, routes of administration, comparative effectiveness, or safety information.

Specific considerations addressed by the program include the following items:

- Assessment of whether the real-life data are appropriate to be used
- Assessment of whether RWE studies generated from these data provide adequate scientific evidence to answer regulatory questions
- Evaluation of whether the studies conducted meet the regulatory requirements established by the FDA.

This approach was developed to serve as a guide for both individual applications and the RWE usage program in general. It also targets standardization in requests and submissions involving real-life data.

The forwarding of a questionnaire to all countries in the region for the purpose of summarizing the characteristics of the local use of RWE will be evaluated. Another alternative would be to fill the questionnaire during or after the PF as additional information for the Report and publication.