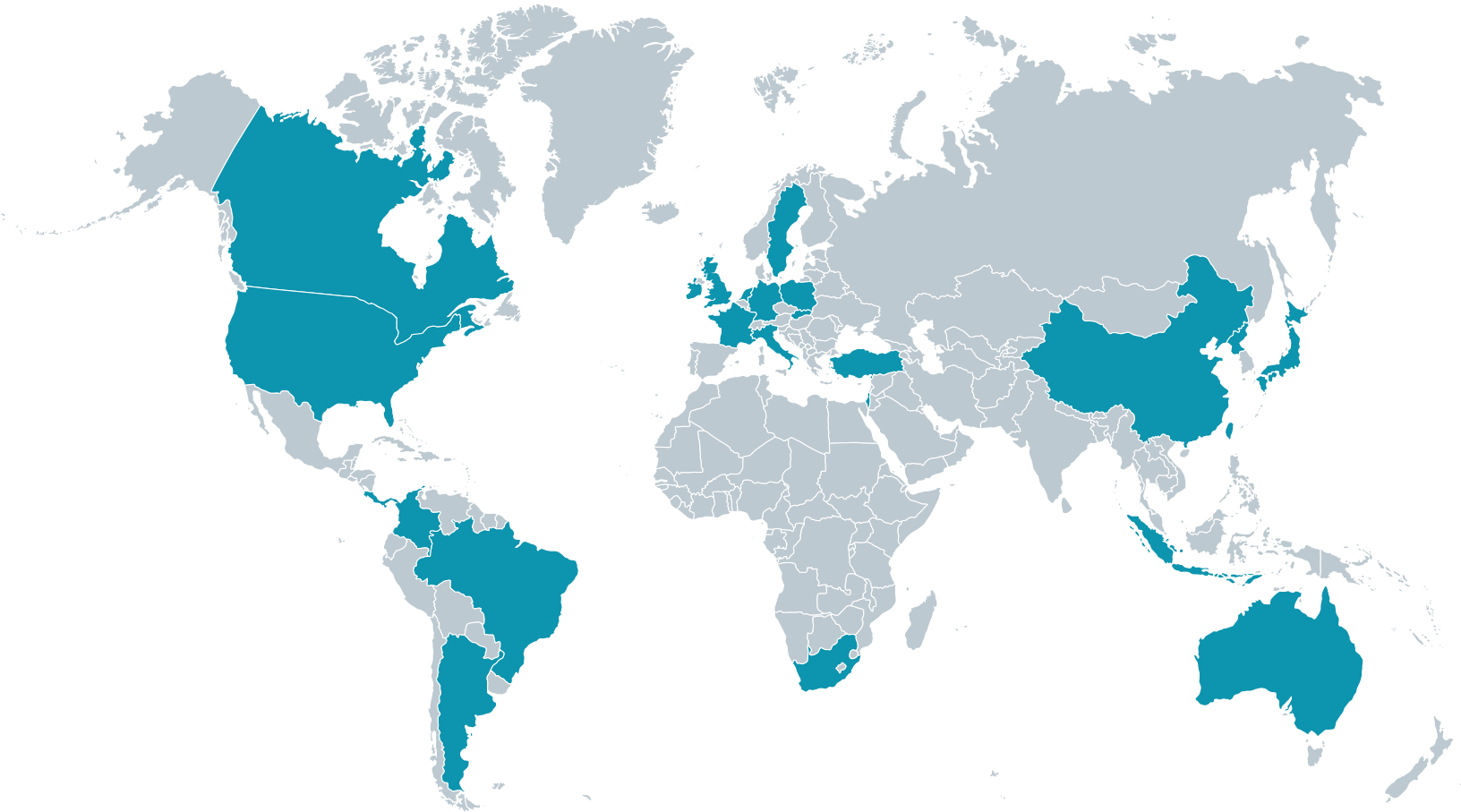
LYMPHOMA COALITION

HEALTH TECHNOLOGY ASSESSMENT

SIMILARITIES AND DIFFERENCES IN MECHANISMS, SYSTEMS AND PROCESSES ACROSS 27 COUNTRIES

2023



About Lymphoma Coalition

Lymphoma Coalition (LC) is a worldwide network of patient organisations with a full or partial focus on providing support to those affected by lymphoma, including chronic lymphocytic leukaemia (CLL). The need for a central hub of consistent, reliable, and current information was recognised, as well as the need for lymphoma patient organisations to share resources, best practices, and policies and procedures. In 2002, four lymphoma organisations started LC and in 2010, it was incorporated as a not-for-profit organisation. Today, there are more than 90 member organisations from over 55 countries.

As the organisation grew, an additional workstream was added dedicated to advocating for equitable care globally. LC's current strategy remains focused on ensuring impact within two key pillars: information and advocacy.

Vision

Equity in lymphoma outcomes across borders.

Mission

Enabling global impact by fostering a lymphoma ecosystem that ensures local change and evidence-based action.

Acknowledgements

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Disclaimer

LC provides the report for general information. The information contained within this report was the result of research conducted during an internship placement in 2023 and is intended to provide an overview of the key findings. While LC makes every effort to ensure accuracy, the information contained in the report is taken from various public sources. No responsibility can be assumed by LC for the accuracy or timeliness of this information.

Contents

Overview

Health technology assessment (HTA) systems for medicines and other health technologies differs widely across countries and regions. The regulatory and HTA landscape is continuously evolving, providing useful learnings and potential opportunities for HTA systems to become more efficient and promote greater involvement of patient organisations.

There is benefit in broadening our understanding of the similarities and differences in key aspects of HTA. It is also important to consider how multidisciplinary perspectives, such as drug development and evaluation, regulatory decision-making, health economics, public policy, and patient involvement, may inform and guide how HTA mechanisms, systems and processes are considered.

Global HTA Mapping

To better understand the global state of HTA mechanisms, systems and processes, LC conducted a comprehensive global mapping and scanning of the HTA landscape across 27 countries. Through this LC explored patient involvement and caregiver input in HTA, guidelines and processes, transparency, provisions and policies for rare diseases, real-world evidence (RWE), inclusion of scientific societies and more.

Purpose

The purpose of the initiative was to gather intelligence and information through public sources to produce an overview of the HTA landscape across the different countries and regions.

Objectives

- Identify similarities and differences in HTA mechanisms, systems, and processes.
- Explore stakeholder involvement in HTA.
- Spotlight HTA practices and processes across countries.
- Provide country examples of best practices in HTA.
- Share some of the challenges and barriers patient organisations experience in HTA.

The report highlights HTA systems for 27 countries in four different regions where LC Members are currently represented, as well as countries where clear similarities and differences in relation to HTA were anticipated. The geographical regions include Asia-Pacific (eight countries); Africa (one country); Europe (twelve countries) and The Americas (five countries). Additionally, the report highlights Turkey with recognition that Turkey is a large peninsular bridging the continents of Europe and Asia.

Table 1: HTA Systems and Processes by Country and Region.

Asia-Pacific	Australia, China, Israel, Japan, Korea, Philippines, Singapore, Taiwan
Africa	South Africa
Europe	Belgium, Denmark, France, Germany, Ireland, Italy, Poland, Slovakia, Sweden, Switzerland, The Netherlands, United Kingdom
The Americas	Argentina, Brazil, Canada, Columbia, United States
Asia and Europe	Turkey

HTA Workshop

In addition to mapping HTA mechanisms, systems and processes, LC explored patient involvement in HTA to understand some of the perceived opportunities, challenges, and barriers from the perspective of LC Members by hosting a HTA Workshop in Madrid, Spain on 19 October 2023. It was attended by Members who have a keen interest and/or firsthand knowledge of HTA within their respective countries.

The workshop was moderated by an external facilitator and ten participants attended in person from China, Colombia, France, Hong Kong, Ireland, Japan, The Netherlands, and Sweden. Additionally, an LC Member from Australia joined virtually for a portion of the workshop.

Objectives

The overall objective of the workshop was to discuss and share some of the best practices that might help increase patient involvement in HTA.

For the first workshop session, participants explored the role of PICO (Patients, Intervention, Comparator, Outcomes) as an important component to defining a HTA research question. To support focused group discussions, four questions were defined:

1. **What is your goal / objective as a patient organisation for giving input?**
2. **What information can you give to the HTA body/agency to ensure they ask the right questions?**
4. **How and from where do you best collect that information?**
6. **What are the key barriers?**

For the second workshop session, the goal was to explore patient data and written HTA submissions. Since many jurisdictions use some form of a submission template to elicit the patient perspective in HTA processes, workshop participants reflected and discussed how best to respond to an HTA submission template and what challenges might be experienced. To support focused group discussions, four questions were defined:

1. **What is your goal / objective as a patient organisation for giving input?**
2. **How can you prepare to collect and summarise the right information?**
3. **Which are the key barriers for giving input through a template?**
4. **Is there anything that should be improved?**

Introduction

Differences at system level can significantly influence the way in which HTA functions including, for instance, whether HTA is integrated into national policies; what mechanisms are in place, and how funding decisions for a new technology are reached.[5]

It is evident that the global HTA landscape is continuing to evolve at a rapid pace and as a result, HTA mechanisms, systems and processes vary considerably across countries and regions. Similarities and differences in HTA may be found across a wide range of areas including the processes that promote and support patient and caregiver involvement; the acceptance and application of RWE; the inclusion of input from clinical experts and scientific societies, and provisions and policies that aim to address rare diseases.

Of the 27 countries highlighted in this report, many have implemented similar processes to ensure patient input is integrated in HTA processes. For instance, Denmark incorporates patient organisation feedback in HTA reports and final conclusions, while Colombia collects patient information through surveys, consensus panels and dialogues. In France, they solicit and gather patient input throughout

the HTA process. In terms of differences, regulatory approvals for countries appear to vary considerably with some countries utilising managed entry agreements, accelerated approval processes, and policy-related initiatives.

New oncology therapies in the pipeline have the potential to improve inequities in access, address unmet patient needs, improve patient outcomes, and impact both decision-making and health spending. The current therapeutic landscape for lymphomas is diverse and complex. Increasingly, there are emerging treatment options for haematological malignancies, including targeted therapies, gene therapies, new drugs or new combinations of drugs, and new delivery techniques. Integrating patient input and experiences in HTA is key to treatment development and in the context of lymphoma highlights the patient experience and provide valuable insights. All of which will help to improve the availability of therapies and support the need for patients to have individualised and timely access to different treatment options for indolent and aggressive lymphomas.

Health technologies that improve outcomes for patients with rare diseases while also supporting health systems and standards of care are essential, including the need for emerging technologies to treat rare diseases[2,3] In the lymphoma landscape, there are over 80 different subtypes of lymphoma, including rare lymphomas such as waldenstrom macroglobulinemia, cutaneous lymphoma, and mantle cell lymphoma. As each subtype of lymphoma has a different clinical course in terms of characteristics, treatment options and care, HTA processes that address unmet patient needs is critical. Additionally, although patient-reported outcome measures (PROMs) are relevant and valuable in HTA to measure patient experiences in terms of both disease and treatment beyond clinical endpoints, it is challenging to develop and administer PROMs for rare diseases. This may be due in part to small patient populations and the implications of short-term studies[4]

There is increased interest from diverse stakeholders to understand and learn about HTA systems. Greater knowledge about HTA mechanisms, systems and processes will benefit diverse stakeholders. Also, helping to bridge existing information gaps and support greater alignment between HTA processes, regulatory decision coverage, and reimbursement decision-making to ensure efficiencies, effectiveness and evidence-based decision-making.

HTA Mechanisms, Systems, and Processes

HTA is a multidisciplinary process that uses scientific methods to determine the value of a health technology and is commonly defined as the "systemic evaluation of properties, effects and/or impacts of health technology with the aim to address quality, value and decision-making on coverage decisions based on "evidence-based information and other socioeconomic factors beyond the clinical and cost-effectiveness of a technology."[5]

Using explicit methods to help inform decision-making and promote an equitable, efficient, and high-quality health system, HTA informs evidence-based decision-making by evaluating the "benefits and efficacy, clinical and technical safety, and cost-effectiveness. Informed decision-making comprises issues surrounding coverage and reimbursement, pricing decisions, clinical guidelines, and protocols" across dimensions that include medical, social, ethical, and economic.

According to the World Health Organization (WHO), HTA mechanisms range from technology assessment and appraisals to supporting decisions on coverage, price negotiation and guidance development. Since the first publication of the Essential Medicines List in 1977, the development of health intervention and technology assessment mechanisms has remained a focus of the WHO.[6]

HTA development has grown substantially from when HTA was a mechanism to support decisions to list or delist pharmaceuticals and devices. With this growth has come a significant increase in the complexity of HTA processes. Today, HTA systems and processes in countries around the world have different mandates and mechanisms, ranging from issuing recommendations for drug reimbursements like that of the Australian Pharmaceutical Benefits Advisory Committee (PBAC), an independent expert body appointed by the Australian Government to recommend new medicines for listing on the Pharmaceutical Benefits Scheme (PBS) or the National Institute for Health and Care Excellence (NICE) that issues recommendations for interventions and the development of clinical guidelines in the United Kingdom.[6]

As health systems around the world become stronger, the continuum of HTA-related activities varies. For instance, based on World Bank country classification, low-income countries with low coverage may have a limited mandate due to factors that include less data intensive methodologies and limited allocation of resources.[1] In contrast, middle income countries with low coverage may look to strengthen resource allocation and methodologies to align with improved data collection. High-income countries, based on the strength of their health systems, are more likely to expand their HTA mandates while sharing knowledge.[1,6]

Figure 1: Technologies and methods considered in HTA. Source: World Health Organization.[6]

Studies that explore the similarities and differences in HTA systems are often viewed from the perspective of coverage decisions, with some reporting that HTA outcomes are not legally binding and others exploring the issue of transparency and whether evidence-based information influences coverage decisions.

In 2022, a study of 32 countries in the European Union, the United Kingdom, Canada, and Australia looked closely at the similarities and differences in HTA systems and Implications for coverage decision, namely how HTA fits into processes such as decision-making, negotiation and funding decisions. The study pointed to significant differences across countries given the dynamic and transformative HTA processes.[5] As HTA comprises different operational practices it is common for the application to differ substantially by setting given that the structure of HTA systems will reflect health system priorities while concurrently underpinning the history, culture, values and preferences of a country[5] Taking into consideration the factors that make HTA processes different across countries, variations may be reflected in different areas including the implementation and impact of HTA on the decision-making process and final coverage decisions.[5] With respect to governance, the study points to independent HTA institutions functioning at arm's length of government, even though some may be part of national healthcare systems. Additionally, HTA systems often mirror the administrative organisational structure, determining whether systems are highly regional or centralised. This can lead to duplication of effort in countries where regional assessment of clinical benefit for a technology occurs, supporting the need for regional cooperation and harmonised mechanisms to streamline activities, methodologies and procedures when assessing health technologies.[5]

Table 2: HTA Process (By Country)

Country	HTA Recommendations	Breakthrough Treatments and Rare Diseases	Pricing and Reimbursement	HTA and Drug Price Negotiations	HTA and Regulatory Reviews
© Lymphoma Coalition	Are HTA recommendations binding or non-binding?	Is there a regulatory approval process for new medicines?	Is the HTA body responsible for pricing and reimbursement?	Are processes conducted in parallel or are they separate?	Is there a concurrent process in place?
Argentina	Unknown	Yes	Not responsible	Unknown	Unknown
Australia	Non-binding	Yes	Not responsible	Unknown	Yes
Belgium	Unknown	Yes	Not responsible	Unknown	Unknown
Brazil	Binding	Yes	Not responsible	Unknown	Yes
Canada	Non-binding	Yes	Not responsible	Separate	Yes
China	Non-binding	Yes	Not responsible	Unknown	Unknown
Colombia	Non-binding	Yes	Not responsible	Unknown	Unknown
Denmark	Non-binding	Yes	Not responsible	Separate	Unknown
France	Binding	Yes	Not responsible	Separate	Yes
Germany	Binding	Yes	Not responsible	Unknown	Yes
Ireland	Non-binding	Yes	Not responsible	Unknown	Unknown
Israel	Binding	Unknown	Responsible	Unknown	Unknown
Italy	Binding	Yes	Responsible	Unknown	Unknown
Japan	Unknown	Yes	Not responsible	Unknown	Unknown
Korea	Binding	Yes	Responsible	Separate	Unknown
Philippines	Binding	Yes	Not responsible	Separate	Unknown
Poland	Non-binding	Yes	Not responsible	Separate	Unknown
Singapore	Non-binding	Yes	Responsible	Parallel	Unknown
Slovakia	Binding	Yes	Responsible	Separate	Unknown
South Africa	Unknown	Yes	Not responsible	Unknown	Unknown
Sweden	Binding	Yes	Responsible	Unknown	Unknown
Switzerland	Binding	Yes	Not responsible	Separate	Unknown
Taiwan	Binding	Yes	Not responsible	Unknown	Unknown
The Netherlands	Non-Binding	Yes	Not responsible	Unknown	Unknown
Turkey	Unknown	Yes	Not responsible	Parallel	Yes
United Kingdom	Binding	Yes	Not responsible	Parallel	Yes
United States	Unknown	Yes	Not responsible	Unknown	Unknown

	Binding, established, responsible and/or parallel processes		Non-binding, not responsible and/or separate processes		Unknown (or too little information available through public sources)

HTA Bodies or Agencies

HTA bodies or agencies perform assessments and play an integral role in the decisions about what technologies should be made available to the public. They may be independent and operate at arm's length of government; integrated within government and decision-making or affiliated with academic institutions.[3]

In the decision-making process, HTA agencies or bodies may have an advisory, regulatory, or coordinating role in the process. More specifically:

Advisory: Responsible to produce coverage recommendations for decision-makers. Recommendations are not required to be considered when negotiating with manufacturers.[5]

Regulatory: Responsible for the pricing and reimbursement of new health technologies. As regulatory bodies are accountable to national health agencies, pricing and coverage decisions are directly impacted.[5]

Coordination: Conduct related research independently, including the evaluation of clinical and economic evidence. Recommendations are rarely considered in coverage decisions.[5]

Additionally, HTA bodies or agencies have different procedures and evidentiary standards that may result in different conclusions, presenting potential implications for access to cancer therapies, including delays associated with duplicative manufacturer submissions (as manufacturers apply before new technology or medicines can be reimbursed and accessible), and varying timelines for national HTA review.[7]

Some countries lack a national approach to HTA. For instance, the United States does not have a national HTA organisation or processes to evaluate health technologies and guide decision-making. Due primarily to the decentralised insurance system where private and public payers independently reach decisions on coverage and negotiate price, there are multiple organisations and/or agencies that assist in HTA and the evaluation of medical interventions.

These include the Agency for Healthcare Research and Quality (AHRQ). AHRQ conducts assessments to help guide coverage and works to "transform healthcare by increasing the quality, availability and use of evidence via scientifically rigorous and unbiased analysis of evidence."[8] Further, the Institute for Clinical and Economic Review (ICER) evaluates new therapies in areas that include the clinical and economic value of prescription drugs, and in 2010, the Patient-Centered Outcomes Research Institute (PCORI) was established.[9] According to the Guide to Understanding Health Technology Assessment (HTA), reports by ICER inform shared decision-making, clinical guideline development, pricing and coverage with reports commonly used by health insurance companies to better understand the benefits, harms, and value of a new technology. Additionally, PCORI, an independent research organisation, was established to empower patients and others with actionable information about their health and healthcare choices.[10]

In Argentina, the HTA system is complex with multiple organisations collaborating and/or operating in the HTA landscape under the auspices of government and academia. More specifically, the Comisión Nacional de Evaluación de Tecnologías de Salud (CONETEC)/ National Commission for HTA and Clinical Excellence is a decentralised body operating under the Ministry of National Health.

In Argentina, CONETEC conducts evaluations and issues technical recommendations of health technologies in areas that include the incorporation, divestment, use and coverage under four different dimensions, namely ethical, medical, economic, and social. CONETEC consults for the entire health system with recommendations binding on the Ministry of National Health.[11] [12]

Additionally, the Unidad Coordinadora de Evaluación y Ejecución de Tecnologías en Salud (UCEETS)/Coordinating Unit for Evaluation and Implementation of Health Technologies is responsible for the coordination of HTA activities across various agencies to support the use of HTA in decision-making at the local and regional levels. Further, from an academia perspective, the Institute for Clinical Effectiveness and Health Policy (IECS) is an independent academic institution dedicated to research, education, and technical cooperation in health care. Affiliated with the Buenos Aires University and the School of Medicine since 2022, IECS created an HTA Consortium of more than 40 institutions to prepare reports about the effectiveness, safety, cost-effectiveness of health technologies and more.[13] Within ICES is an agency for HTA that prepares different types of documents, reports, systematic reviews, and economic evaluations to inform decisions about health insurance, refunds, and health technology investment.[13]

It should be noted that in countries that have no formal national HTA institution at present, such as **South Africa**, systems have allowed for and/or have implemented several processes that aim to use elements of HTA to inform access to a health technology as well as help inform decisions regarding healthcare resource allocation.

Table 3: HTA Body or Agency by Country (links where available)

Country	Name of Primary HTA Body or Agency
Argentina	National Commission for Health Technology Assessment and Clinical Excellence
Australia	Australian Government, Department of Health, and Aged Care
Belgium	Belgian Health Care Knowledge Centre (KCE)
Brazil	National Committee for the Incorporation of Technologies in the Unified Health System (CONITEC)
Canada	Canadian Agency for Drugs and Technologies in Health (CADTH) National Institute of Excellence in Health and Social Services (INESSS
China	The National Center for Medicine and HTA (under the China National Health Development and Research Center (CNHDRC)
Colombia	Institute of HTA (IETS)
Denmark	Danish Centre for Evaluation and HTA (SST) – Danish Medicines Agency
France	French National Authority for Health (HAS)
Germany	Institute for Quality and Efficiency in Healthcare/Institut für Qualität und Wirtschaftlichkeit im Gesundheits-wesen) (IQWIG)
Ireland	National Centre for Pharmacoeconomics (NCPE)
Israel	Division for Assessment of Technology in the Health Basket (Ministry of Health)
Italy	Italian Medicines Agency (AIFA)
Japan	Central Social Insurance Medical Council (Chuikyo) (CSIMC)
Korea	Health Insurance Review and Assessment Agency (HIRA) National Evidence-based healthcare Collaborating Agency (NECA)
Philippines	HTA Council (HTAC)
Poland	Agency for HTA and Tariffication/Agencja Oceny Technologii Medycznych i Teryfikacji (AOTMIT)
Singapore	Agency for Care Effectiveness (ACE)
Slovakia	Slovak Ministry of Health: Working Group for Pharmacoeconomics, Clinical Outcomes and HTA of the Slovak Ministry of Health
Sweden	Pharmaceutical Benefits Board/Tandvårds-Läkemedelförmånsverket (TLV)
Switzerland	The Foundation for Technology Assessment (TA-SWISS)

Country	Name of Primary HTA Body or Agency
Taiwan	Center for Drug Evaluation (CDE)
The Netherlands	National Healthcare Institute/Zorginstituut Nederland (ZIN)
Turkey	Social Security Institution (SOSYAL GÜVENLİK KURUMU; SGK) (SSI)
United Kingdom	National Institute for Health and Care Excellence (NICE)

In addition to individual country HTA bodies or agencies, there are also regional and global networks that serve to promote knowledge and information sharing and to strengthen HTA capacity by sharing HTA information, experiences, and resources, and collaborate to enable patient access to medicines.

- Globally, the International Network of Agencies for HTA (INAHTA) is comprised of more than 50 HTA agencies working together to share information and support the production and dissemination of reports for evidence-based decision-making.2 INAHTA maintains an international HTA database that serves as a single point of access to information about ongoing and published HTAs undertaken by HTA agencies or organisation.

- In Europe, the European Medicines Agency (EMA) has been working with regional and national HTA organisations that provide recommendations on reimbursement. A 2021-2023 work plan between EMA and the European Network for HTA 21 (EUnetHTA 21) includes, "joint scientific consultation for robust evidence generation, exchange of information on assessments of medicines and generation of patient-relevant data and information to support decision-making."[3] [14]

- In Asia-Pacific, HTAsiaLink addresses the regional need to strengthen HTA capacity and promote the use of HTA evidence in policy decisions. Organisational members include HTA institutions, government HTA units who are involved in HTA research and evidence-based policy decision-making in the Asia-Pacific region and individual members include researchers, academics, and professionals.

- The Health Technology Assessment of the Americas (Red de Evaluación de Tecnologías en Salud de las Américas – RedETSA) network was launched in 2011 and since then, has grown significantly. RedETSA is comprised of 39 institutions from 19 countries as of December 2021. RedETSA member institutions developed a centralised single platform or regional database of HTA Reports in the Americas, the Base Regional de Informes de Evaluacion de Tecnologias en Salud de Las Americas (BRISA). The Pan American Health Organisation (PAHO), the agency that serves as the network Secretariat, noted an increase in the number of BRISA users from the initial launch to 2021.[15]

Stakeholder Involvement in HTA

Patient and Caregiver Involvement

Patient involvement in HTA helps to incorporate the priorities of the patient population, including real-life experiences with the disease and available therapies. The consequences of therapy regimes on daily life, and what 'trade-offs' patients would be willing to accept, into HTA considerations. As the patient viewpoint may differ from clinical or research perspectives, patient involvement in HTA afford the opportunity to provide context in relation to what the intervention would mean to them; what their experiences are; what the real-life comparator is; and the outcomes that are valued as most important.

Lymphoma Coalition (LC) research found there is insufficient time allowance for patient organisations interested in participating in the HTA process to collect data when the call for input comes from the respective HTA body or agency. It is therefore essential that patient organisations prepare their respective HTA submission as early as possible. The most convincing and representative input from patients in HTA is evidence and data collected from a broader group of patients. Early engagement in HTA helps to ensure targeted evidence needed to demonstrate the value of a new medicine for patients can be gathered or generated.

In the lymphoma landscape, Lymphoma Coalition collects comprehensive global data every two years through the LC Global Patient Survey on Lymphomas & CLL (GPS). Launched in 2008, the GPS seeks to understand patient experience in lymphomas as well as the impact of treatment and care with the results used to ensure patient voices are heard, and to help drive planning, actions and support.

In 2022, the GPS was available in 19 languages. There were 8,637 completed responses across 72 countries, made up of 7,113 patients and 1,524 caregivers. A total of 18 countries had over 100+ responses with the largest global regional distribution (where patients responded from) from Europe (49%), followed by Asia-Pacific (31%) and North America (18%). The distribution for South America and Midde East and Africa was 1% respectively. Globally, the top four country responses were from France (18%), China (15%), United States (13%) and Italy (7%). [16]

The GPS research themes for 2022 included information and guidance, healthcare support, healthcare involvement and decision-making, effects of lymphoma, treatment experience and side effects of treatment. The GPS report captures information that may be used to provide valuable information and data for HTA submissions by patent organisations. For instance, analysis by indication to understand patient experience with current therapies, information specific to subtypes of lymphoma, short and long-term adverse events, the impact on quality-of-life, psychosocial concerns, and barriers to care.

Results of the GPS may be used to provide valuable information and data for HTA submissions from patient organisations. GPS data is used by LC to publish research papers, conference presentations and posters, and global reports such as the 2023 Psychological Impact of Lymphoma white paper; 2022 Report Card on Lymphomas: Spotlight on the Experience of Patients with Indolent Lymphomas and 2022 Lymphoma Care in Europe Reflections on Patient Experience and Priorities for Care report.

In addition to the limited time patient organisations have to prepare an HTA submission, there are other factors that may influence, impact, and/or impede their involvement. During the 2023 HTA Workshop hosted by Lymphoma Coalition, some considerations included:

- The significant demand on patient organisations in terms of capacity and resources.
- The complexity of language used in HTA reports and/or relevant documentation and the corresponding need for information to be available to patient organisations in plain language.
- The lack of feedback from HTA bodies or agencies to patient organisations regarding their submissions to fully understand its impact.
- The need to ensure the patient voice is reflected when assessing the value of a new medicine which, in some cases, could be an additional treatment option.

Additional factors that patient organsiations may have an interest in addressing in a submission where feasible, such as the burden of cost, overall survival, and improved quality-of-life.

Unquestionably, patient involvement in HTA across diseases is critical to ensuring new interventions and technologies are approved and available to patients and plays a key role in helping decision-makers define how patient input is considered, valued, and integrated in HTA. Patient involvement throughout the process of HTA offers opportunities to inform researchers, healthcare decision-makers and policymakers about patient experiences, expectations, needs, and preferences in the context of living with a disease and/or using a specific technology.

Although processes to involve patients in HTA is evolving in many countries and regions, the degree or level of patient involvement still varies considerably. Factors such as the capacity and/or level that patient organisations may become involved; opportunities for patients to become more engaged and/or the processes and mechanisms to support involvement are all key considerations.

Some countries promote patient involvement by ensuring patient representatives serve on advisory boards and/or are represented in HTA to provide the patient voice. These countries include **Brazil**, **Germany**, **Japan**, **Taiwan**, **Turkey, Singapore**, and **Sweden**. In addition, some countries, like Brazil, promote patient participation during the initial meeting for technology evaluation.

Despite increased levels of patient involvement in HTA, limitations and/or barriers remain.[17]While **China** recognises patient involvement in HTA, guidelines or procedures to support engagement are lacking.

In **Korea,** patients are rarely included in the HTA submission process due to a general lack of transparency, feedback on the process and support from HTA bodies or agencies. According to a 2021 survey of patient advocacy groups, respondents from South Korea (n=8) reported the most common reason for not providing input to HTA was a lack of awareness about opportunities to do so. Additionally, three respondents from **South Korea** shared that they had prior experience providing patient input for assessment processes and the type of input provided included preparation of input to the HTA body or agency; participation as a committee member, feedback on draft recommendations, collection and/or reporting of information to inform input, and provision of information to patients about how patients can provide input to the process.[18]

In countries where HTA systems are advanced and/or more established, input from caregivers is encouraged and valued. This includes the countries of **Belgium**, **Canada**, **Germany**, **Sweden**, Switzerland, **United Kingdom,** and the **United States.** Other countries, such as **Singapore,** empower caregivers to participate by providing access to tools, resources and information about medical conditions and treatment options.

To support the involvement of patients, caregivers, and patient groups, **Taiwan** published guidelines to help express opinions on an online platform to gather information including methods of information gathering; experiences of living with a condition/disease; experiences of traditional and/or new treatments; expectations regarding new treatments and effects on caregivers with/without the new treatments.[22]

Additionally, some countries - like **Argentina** - conduct a public consultation process for HTA reports with comments analysed and considered from the moment of defining the research question until the publication of the final HTA report.[19]

Scientific Societies in HTA

Many countries involve healthcare professionals and scientific societies in the HTA process to seek their input in assessments and reporting, as well as contributions to public health information and the evaluation of the impact of health technologies on care pathways.

Involving healthcare professionals and scientific societies in health technology assessment processes is essential as they bring valuable expertise and insights on the impact of health technologies. Representing the broader healthcare and scientific communities, they also ensure clinical relevance and practical implications are considered and contribute to ethical discussions on the use of health technologies.

Of the 27 countries highlighted in this report, the majority of countries (21) report the inclusion of scientific societies in HTA processes. Namely: **Australia**, **Belgium**, **Brazil**, **Canada**, **China**, **Columbia**, **France**, **Germany**, **Ireland**, **Israel**, **Italy**, **Japan**, **Philippines**, **Singapore**, **South Africa**, **Sweden**, **Switzerland**, **The Netherlands**, **Turkey, United Kingdom**, **United States**. It is unclear whether **Denmark**, **Poland**, **Slovakia**, **Taiwan**, and **South Korea** formally include scientific societies. At present, **Argentina** does not appear to formally include scientific societies in HTA.

There are different avenues to involve scientific societies. For instance:

- **The Netherlands** engages a Scientific Advisory Board to support HTA. Additionally, the National Health Care Institute serves as an advisory and implementing organisation that performs activities, including advising on the contents of the standard health care benefit package and assessing outpatient medicines for the benefit of the Medicine Reimbursement System. (GVS)[20]

- Other countries, such as **China**, support healthcare providers using a hospital-based approach to HTA or by engaging healthcare providers at specific stages of the HTA process.

HTA Processes and Best Practices

Processes to promote patient and caregiver involvement in HTA vary significantly across countries, systems, and regions.

In **Australia**, HTA processes allow for public involvement in HTA processes. More specifically, patients share experiences about current treatments or new technologies; caregivers provide feedback on recommendations, and health care professionals and scientific societies assist HTA bodies to better understand the benefits and challenges of current or new treatments. There are various ways for the public to be involved in the HTA process, ranging from providing input on applications and comments on applications for new medicines, medical devices and health technologies to avenues that allow for the inclusion of patient experiences in relation to adverse events. Further, comments on applications for public subsidy of new health technologies are submitted using the Australian Government Department of Health and Aged Care, Office of HTA (OHTA) consultation hub.

Brazil considers patients and patient groups as key stakeholders, considering real-life experiences as well as patient expectations and points of view as helping inform the decision-making of HTA agencies, ANVISA and CONITEC. In Brazil, patient involvement is encouraged during the initial Patient Participation in Initial Appreciation Meeting for Technology Evaluation. Additionally, the Patient Perspective Guidelines provides opportunities for enhanced citizen engagement.

Canada values patient perspectives to improve the quality of assessments and offer insights on patient needs, supported by a Framework for Patient Engagement in HTA. In addition to patient perspectives, Canada involves families and patient groups to ensure that those affected by the assessments have an opportunity to contribute. Canada has also established Standards for Patient Involvement in HTA Processes that are publicly accessible.

The Philippines allows patient perspectives on the disease experience and patient-related outcomes that matter most to them, and invites patient insights on the use of new and existing treatments through testimonials and written submissions for consideration by the HTA Council (HTAC).

Singapore follows the Agency for Care Effectiveness (ACE) Process and methods guide for patient involvement to highlight the contributions that patients and caregivers can make by providing valuable experiential knowledge of different medical conditions and health technologies, sharing what outcomes are considered most important to them.

Following the 1995 National Health Insurance (NHI) program, Taiwan introduced HTA processes in the second generation of the National Health Insurance Act 2 that established HTA processes and ensured that patient groups could participate in pharmaceutical benefits and reimbursement scheme committee meetings. In 2015, Taiwan launched an online platform allowing patients, caregivers, and patient groups to provide insights on new drugs or medical devices by answering a series of questions that include experiences with treatment and expectations regarding new treatments.22 Patient input is summarised and incorporated in HTA reports which are then published before the Pharmaceutical Benefits and Reimbursement Scheme (PBRS) Committee meetings to allow for greater understanding and learning of patient experiences in relation to the health technology.22 Additionally, patients have the option to

attend the PBRS meetings as well as pre-meetings to discuss patient perspectives in advance. For resubmission cases, the PBRS allows two disease-specific patient representatives to attend and share their opinions. From 2015 to 2020, 30 patient inputs were published prior to PBRS Committee meetings, with 19 (63%) related to oncology.[22]

In Europe, many countries have developed guidelines, processes, and mechanisms to support and promote patient involvement.

- **Belgium.** Established standards for patient involvement and allows caregivers to provide feedback in the research process.

- **France.** Solicits and considers patient input throughout the HTA process, with the Public Involvement Council collaborating with stakeholders to enhance engagement through digital connectivity. Additionally, France allows patient input submissions before committee meetings, involving patients at the step of advice and decision-making, and in the HTA of medical devices and other technologies.

- **Germany.** Encourages patients to submit comments and engage in discussions with the regulatory agency. Further, patient participation is encouraged in the Federal Joint Committee with the processes overseen by the German Federal Joint Committee (G-BA).

- **Ireland.** Supports patient involvement by promoting knowledge about medicines development and regulatory processes by means of the National Centre for Pharmacoeconomics Ireland (NCPE) Patient Education Program.

- **United Kingdom.** The National Institute for Health and Care Excellence (NICE) Public Involvement Programme prioritises the involvement of consumers, service users, the public and community organisations in the development and implementation of guiding documents. Further, the Patient and Public Involvement Policy defines numerous areas, including available support to those individuals and organisations involved in the work of NICE based on two key principles: (1) Opportunities exist to contribute to developing guidance, advice and quality standards to support implementation. (2) There is a greater focus and relevance for those most directly affected by recommendations.

- **The Netherlands.** Patient organisations are involved in HTA processes, typically at the appraisal stage of HTA as providers of submissions.[24]In 2022, a study analysed all drug assessments by the public HTA agency that were conducted in 2019. The study included interviews with employees of the HTA agency and representatives from both patient organisations and medical associations. In almost half of the assessments, the study found that no patient organisations were involved at the start of the relative effectiveness assessment. Further, although patient organisations and medical associations were asked to comment on draft reports, the short 5-day response period used by the HTA agency was reported to negatively impact both response and involvement.[25]

Training and Resources

To encourage and support patient and public involvement in HTA processes, some countries provide access to specialised training, tools and/or resources.

In **Canada**, participants in HTA (including researchers, staff, reviewers, and committee members) receive training on the involvement of patients and the integration of patients' perspective in the HTA process. Additionally, patients and patient organisations also have an opportunity to participate in training that includes webcasts delivered through a lecture series.

First introduced in 2016, **Italy** provided training aimed at civic leaders and operators of the National Health Plans and for those involved in HTA processes to promote citizen and patient involvement in HTA. and policy documents to promote patient involvement. It was anticipated that training would help to facilitate knowledge sharing and help increase functional skills to support involvement and the collection of patient evidence.

In 2016, **Taiwan** established a patient involvement taskforce and launched educational programs to introduce HTA, the reimbursement processes and mechanisms to support patient involvement and in 2018, developed instructions to patients, caregivers and patient organisations on how to use the Taiwanese online submission platform managed by the National Health Insurance Administration (NHIA).[22 23]

HTA Systems and Processes

Transparency

Transparency in HTA processes helps to ensure relevant information is accessible to stakeholders in addition to ensuring that decision-makers have the opportunity to consider the perspectives of patients, caregivers, and the public to help inform decisions that align with societal preferences.

Some HTA agencies impose restrictive measures that reflect or take into consideration different weights given to data sources that may delay patient access. For instance, while the National Institute for health and Care Excellent (NICE) in the United Kingdom focuses on cost-effectiveness other countries, such as Germany and France, focus more on comparative effectiveness.[26] France, Germany and the United Kingdom all publish details about reimbursement decisions, namely the rationale.[26]

According to a cross-sectional study in 2022, it was suggested that patients in the United States have access to new oncology therapies earlier that in Europe. the median delay in Europe market authorisation for new oncology therapies.[27] This timeline may include the initial submission of the drug dossier, evidence evaluation, health economic assessments, stakeholder consultations, and final decision-making. Some countries do not provide concise or detailed information on the duration of HTA completion in relation to oncology drugs. These include **Argentina**, **Australia**, **Belgium**, **Brazil**, **Canada**, **China**, **Colombia**, **Denmark**, **France**, **Germany, Ireland**, **Israel**, **Italy, Japan**, **Poland**, **Singapore**, **Slovakia**, **South Africa**, **Sweden**, **Switzerland**, **The Netherlands**, **Turkey**, **United Kingdom**, and the **Philippines**. Only four countries - **Italy**, **Korea**, **Tawain,** and the **United States** – appeared to provide clear and accessible information about the average completion time for HTA assessments of oncology drugs.

In **Taiwan**, the approval rate of cancer drugs was lower than non-cancer drugs (approval rate of cancer drugs, 55%; non-cancer drugs, 60%). Among the approved cases, the median time to approval was longer in cancer drugs (18.77 months), compared with non-cancer drugs (9.67 months).[28]

In **Australia**, HTA review processes show improved transparency, including the publication of MSAC Public Summary Documents. To further enhance transparency in the country, HTA recommendations include a centralised website for public access to assessment-related information. This is also evidenced in **Belgium** where HTA bodies proactively publish reports and recommendations on their websites, providing transparency regarding the HTA process and the evidence utilised.

In **China,** the National Health Commission proposes an independent third-party HTA to enhance healthcare quality, highlighting the need for monitoring and standardised procedures. While transparency and publication of HTA decisions are not explicitly mentioned, the focus on information disclosure and peer monitoring suggests potential consideration of these factors.

Other countries have also implemented measures to promote or increase transparency. For example:

- **Colombia.** HTA bodies proactively publish reports and recommendations on their websites, providing transparency regarding the HTA process and the evidence utilised.

- **Singapore.** ACE prioritises transparency and credibility in HTA by mandating disclosure of financial conflicts of interest for patient or carer input. They enhance transparency by publishing key technical evaluations in scientific journals and actively sharing scientific content at regional and international symposiums and conferences.

- **Taiwan.** The CDE collaborates with agencies and patient groups, involving patients in HTA through online sharing of experiences and including their input in reports, with published meeting documents and recordings on the NHIA website to ensure transparency and interdisciplinary deliberations.

- **South Korea.** HTA agencies prioritise transparency by implementing transparent decision-making processes, providing clear guidelines for sponsors, and ensuring impartiality and independence in their HTA processes.

- **Slovakia.** Guidelines for HTA preparation in Slovakia are publicly available. Participants in the process are encouraged to disclose conflicts of interest, safeguarding credibility, and ensuring objectivity in the reports.

- **Turkey.** Guidelines for HTA preparation are publicly available. Participants in the process are encouraged to disclose conflicts of interest, safeguarding credibility, and ensuring objectivity in the reports.

- **Philippines.** The HTA process in the Philippines adheres to transparency standards set by the Department of Health, ensuring accountability and efficiency through clear timelines, in line with policymakers' decision-making and patient needs.

Real-World Evidence and Real-World Data

Globally, the inclusion of real-world evidence (RWE) and real-word data (RWD) in HTA is increasing. According to the Canadian Agency for Drugs and Technologies in Health (CADTH) potential sources of RWD might include healthcare records, registries, and insights from patients.[29]

There are several countries that integrate RWE in HTA. **China** follows guidelines for the use of RWE in drug research and development; **Italy** values RWE as insights into drug usage, patient characteristics and patient safety. **Singapore** incorporates RWE and aligns regulatory and policy approaches to help increase timely access to medicines. Lastly, in terms of how, **Taiwan** uses RWE in drug research and development and as technical documents for drug review applications.

In **Canada**, CADTH recently partnered with Health Canada, the Institut national d'excellence en santé et en services sociaux (INESSS), and other health system stakeholders to advance the integration of RWE into decision-making. The document, Guidance for Reporting RWE helps to establish a foundation for the use of RWE in regulatory approval and HTA, beginning with the principles for transparent reporting of RWE studies.

While clinical trials are the gold standard for evaluating safety and efficacy under controlled conditions, the resulting evidence has some limitations. For instance, due to eligibility criteria, the patient population in the trial may not reflect a realistic range of patients including multi-morbidities. all age ranges, and/or specific sub-populations.

Although study endpoints are measured in the trial setting, endpoints may not accurately reflect the real-world setting. In some disease areas, it may be difficult to recruit a large enough patient population to reveal significant and relevant differences between different treatment schemes. As well, special considerations for rare disease may allow for manufacturers to file based on phase II data that does not include a comparator arm. While RWE cannot replace randomised controlled trials (RCTs), there is potential for RWE to help address knowledge gaps found with interventional trials.

RWD are collected in many places in healthcare, including electronic medical records, patient registries, or by using questionnaires. By formulating a research question and developing a study protocol, RWD can be used to address the question through data analysis, generating valuable and relevant RWE. While RWE is usually observational and non-interventional, the evidence can compare the impact of interventions in real-life use by appropriately selecting and extracting from patients using (or not using) the intervention. This ensures that the resulting study populations are meaningful to answer the research question and to avoid biases that may be introduced by other factors.

In addition to the risk of data biases, there are other factors that may impact the quality of such observational research with RWD. These include limitations in data quality, data completeness, or data privacy. Although such data could enhance the quality and relevance of HTAs, the use of RWE is limited with a lack of guidance and consensus on how the evidence can be used. There is much development in this area, especially in areas where RCTs are difficult and/or do not reflect the real-life usage well.

As the use of expedited pathways and highly innovative technologies may mean that some health technologies enter the market with limited evidence to demonstrate clinical effectiveness. There are "divergent views on the potential of RWD to inform decisions made by regulators, HTA bodies, payers, clinicians, and patients and how RWD is used to generate evidence to inform decisions."[30]

Examples where clear processes that value and support the integration of RWE in HTA include:

- **Canada.** Health Canada values RWE for decision-making on rare disease drugs due to limited patient populations for clinical trials. In collaboration with Health Canada and the Institut national d'excellence en santé et en services sociaux (INESSS), CADTH produced the Guidance for Reporting RWE (May 2023) to help define the use of RWE in regulatory approval and HTA processes in the country. The document also includes a Recommendations Checklist tool to help ensure submissions adhere to the guidelines.

- **China.** In 2020. the National Medical Products Administration (NMPA) introduced Guidelines for RWE to Support Drug Development and Review help to ensure quality and efficiency. These were supplemented by the Guidelines for RWD Used to Generate RWE from CCFDIE in 2021.

- **Korea.** RWD sources like electronic medical records, insurance claims databases, and registries offer valuable insights for research. The Korean National Health Insurance Service database is a comprehensive source of RWD, enabling studies on cost-effectiveness, long-term follow-up, and generalisability.

- **The Netherlands.** RWD for assessing clinical effectiveness is accepted in The Netherlands, alongside randomised controlled trial (RCT) data as the primary evidence. RWD is considered supplementary, and its incorporation depends on its ability to fill evidence gaps and adherence to study protocols. The Netherlands has established the Scientific Advisory Board (WAR), consisting of healthcare experts, to offer scientific guidance on package management duties and ensure quality.

- **Taiwan.** Collaborates with agencies and patient groups, involving patients in HTA through online sharing of experiences and including their input in reports, with published meeting documents and recordings on the NHIA website to ensure transparency and interdisciplinary deliberations. The Taiwan FDA has developed guidelines, including "Basic Considerations for RWE to Support Drug R&D" and "Precautions for Using RWD/RWE in Drug Review Applications," to provide guidance on utilising RWE in drug research and development and as technical documents for drug review applications.

- **United States.** The Food and Drug Agency (FDA) is committed to the full potential of fit-for-purpose RWD to generate evidence that advances the development of therapeutic products and strengthen regulatory oversight. In 2018, the FDA created a Framework intended to help generate data supporting new indications and post-approval study requirements for drug and biologic review programs. [31]

A lack of urgency to adopt RWE, insufficient knowledge or awareness about RWE, and limited experience conducting observational or non-interventional research might be some of the underlying contributors to some countries without RWE guidelines in place. For instance:

- **Poland.** Currently, Poland lacks a process or recognised framework for incorporating RWE and RWD within HTA processes. There is a growing need for more evidence to allocate limited resources, but RWE has not been fully embraced by key stakeholders.

Additionally, limited access to data that meets RWE criteria poses a barrier, as existing medical data sets are primarily maintained for settlement purposes with the National Health Fund (NFZ).

- **Germany.** IQWiG and the Belgian HTA agency KCE challenge the prevailing use of RWD for drug approvals, advocating instead for efficient RCTs in challenging areas. They propose integrating RWD into RCTs, emphasising patient involvement and knowledge dissemination, and calling for an expanded definition of RWD to include RCTs, following the FDA example in the United States.

- **Singapore.** While the ACE does not provide specific guidelines for RWD generation and RWE utilisation in HTA, ISPOR-S in Singapore works with HTAsiaLink and others, such as the Saw Swee Hock School of Public Health and industry, to support regional guidelines for evidence generation and collection, forming a working group and international advisory committee to support this effort. In Singapore, the HTA body called The Agency for Care Effectiveness (ACE) is responsible for pricing and reimbursement however, ACE is part of the Ministry of Health.

Additionally, there are several countries exploring the importance of RWE or implementing RWD. For instance:

- **Denmark**. Several studies have explored the application and implementation of RWE in the context of healthcare. One study evaluated the effect of new medicines for lung cancer patients. The study emphasised the necessity of updated information regarding the real-world impact of new treatments on patients' work productivity, life expectancy, and the potential effects on their close relatives, highlighting the importance of considering broader societal perspectives when evaluating the impact of medical interventions. [32]

- **Japan.** While not unique to Japan, some of the challenges for RWE and RWD in the country include restricted access and linkage of RWD, as well as the lack of universally accepted methodological approaches. While there has been progress in utilising RWD in some cases, it remains insufficient. Future developments with respect to RWE and RWD in Japan are likely to focus on improving access to data, data linkage, more acceptance of data by decision-makers and innovation in terms of supporting technology.[33]

- **Sweden**. In Sweden, an exploration of the value of RWD from Swedish registries to further understanding prostate cancer risk and improving clinical care highlighted the significance of the National Prostate Cancer Register (NPCR) and the Prostate Cancer data Base Sweden (PCBaSe) in driving clinical research and enhancing the utility of RWD specific to prostate cancer studies.

- **Switzerland.** Swissmedic closely monitors global advancements in the regulation and use of RWD and RWE, such as the FDA Sentinel System and DARWIN EU. In Switzerland, therapeutic product legislation requires results of good clinical practice (GCP) compliant clinical trials. According to the Swissmedic position paper on the use of real world evidence, they conclude that "RWE is regarded as a supplemental tool to support marketing authorisation, especially in rare disease settings where there is a high unmet medical need" and their collaboration with partners and regulatory authorities to evaluate the significance of RWD/RWE in guiding therapeutic decision-making in the country.[34]

Breakthrough Treatments and Rare Diseases

Rare diseases affect millions of people.[35]With the incidence of rare disease increasing annually, the number of rare disease patients worldwide is nearly 400 million and between 6,000 to 8,000 unique rare diseases have been identified which are often chronic, progressive, and debilitating. A 2022 comparison o HTA decision-making processes across countries noted that limited evidence on clinical and cost-effectiveness, as well as small patient populations and disease heterogeneity, may challenge traditional HTA, reimbursement and pricing processes with respect to drugs for rare diseases.[36]

In the lymphoma landscape, there are more than 80 different indolent and aggressive subtypes, each with different diagnostic evaluation, treatment protocols, characteristics, indications, sub-populations, and outcomes. Lymphoma subtypes are often categorised into groups that may be confusing to patients. While there have been great strides in rare disease research and the global policy landscape, a general lack of public awareness may contribute to the marginalisation of the rare disease population, including patients with rare lymphomas, in health systems and related policies.[37]

In recent years, many countries have implemented rare disease plans to produce policies that promote research, improve access, and increase awareness.[35]From a policy perspective, rare diseases are continuing to gain momentum with a multistakeholder commitment to ensuring rare diseases are globally reflected in Universal Health Coverage as addressed in 2023 at a formal side event of the United Nations Meeting on Universal Health Coverage 2023.

Many countries have prioritised rare diseases in their national health agendas and/or established national rare disease plans with initiatives to address the unmet needs of patients in the rare disease space. For instance, **Belgium** implemented bilateral agreements with other countries to help assess the value of orphan drugs and negotiate prices.

Additionally, in March 2023, the Government of Canada announced as part of the first-ever National Strategy for Drugs for Rare Diseases an investment of funds as part of a national governance structure to support implementation of the strategy and help improve access and affordability of drugs for rare diseases across the country. More recently, **Canada** announced the creation of the Implementation Advisory Group to establish "a forum for patient and stakeholders to provide patient-centred advice and exchange rare diseases-related information, as well as best practices that will assist the implementation of the National Strategy."[38]

Table 4: Provisions and/or Policies to Address Orphan Drugs or Rare Diseases (by Country)

Country	Provisions and/or Policies at Country Level
Argentina	In 2021, the Argentinian Ministry of Health issued Regulation No. 641/2021 which approved a list of rare diseases according to prevalence in the country. Regulation No. 4,622/2012 states that, "Orphan Drugs are those intended for the prevention, diagnosis and/or treatment of rare diseases."
Australia	The Strategic Agreement between the Australian Government and Medicines Australia aims to enhance patient access to advanced therapies, particularly for rare diseases. It involves reviewing HTA policies to address the access gap for rare disease treatments and prioritises timely and equitable patient access to new cancer medicines. The 2020 National Strategic Plan for Rare Diseases outlines the principles and actions for Australians living with a rare disease.
Belgium	Orphan drugs are fully reimbursed incentives to support rare diseases and orphan drugs exist in Belgium. These include bilateral agreements with other countries to assess the value of orphan drugs and negotiate prices, as well as measures such as waiving regulatory fees for orphan medicinal products and providing an early access procedure for unmet medical needs.

Country	Provisions and/or Policies at Country Level
Brazil	The Brazilian Health Surveillance Agency (ANVISA) and its General Management of Drugs and Biological Products (GGMED) oversee the registration process for orphan drugs in the country. The requirements include submitting a technical assessment report from regulatory authorities if the drug is already approved in other countries. Imported drugs may have waived quality control provided the quality control is performed by the manufacturer. For rare disease drugs with incomplete clinical development, a clinical report can be submitted to ANVISA.[39]
Canada	In Canada, drugs for rare diseases are authorised for sale under the Food and Drugs Act. The Regulatory Review of Drugs and Devices Initiative in Canada makes regulatory processes more efficient in consideration of the needs of challenges of Canadians with rare diseases. In January 2021 Health Canada launched an online engagement initiative to invite Canadians (especially those with a rare disease and their families) to share their respective views and ideas for a national rare diseases strategy based on the discussion paper, Building a National Strategy for High-Cost Drugs for Rare Diseases: A Discussion Paper for Engaging Canadians.
China	China implemented a national system for rare diseases to enhance medical treatment, insurance, and medicine supply. The List of Drugs Covered by National Medical Insurance that covers, under basic medical insurance, was updated to reflect an increasing number of drugs to treat rare diseases. As well, the introduction of policies by the National Medical Products Administration to expedite drug registration and support research and development in the field of rare disease drugs.[40]
Colombia	In 2010, Colombia introduced legislation (Law 1392, enacted July 2010) to support the rare disease community and increase access to orphan drugs, with a 2014 resolution including a mandate to include a representative from the Colombian Federation of Rare Diseases establishing a precedent for patient advocates to work with government officials and physicians on the development of rare disease policy. Between 2012 and 2018, at least 6 national regulations specific to rare diseases were implemented and in 2018, the Health Ministry issued a resolution to establish diagnostic and treatment reference centers in existing healthcare institutions for rare disease patients. [41]
Denmark	Denmark implemented a National Strategy for rare diseases with a five-year perspective.[42]The strategy includes plans for monitoring and evaluating its effectiveness after 3 to 5 years. The Danish Health Authority and the National Board of Social Services conduct status evaluation to assess the progress of the National Strategy, providing a comprehensive report on rare disease efforts in Denmark.
France	France grants access to advanced therapy medicinal products that have achieved ASMR level (the "determination of the medical benefit a product offers over current standard of care") as granted by the French National Authority for Health that allow for central reimbursement on the liste en sus.[43]Additionally, in 2020 France unveiled the Innovative medicines assessment action plan to help improve the overall assessment process. Key areas within the plan include issuing conditional reviews, monitoring medicines in real-life conditions, reinforcing the agility of HAS to support innovation, involving patients and consumers, improving transparency, and sharing knowledge.
Germany	In 2013, Germany adopted and implemented a National Plan of Action for People with Rare Diseases, which outlines specific action fields and goals to address the needs of individuals affected by rare diseases. There are more than 30 centers for rare diseases in Germany with primary care physicians key in the care of patients with rare diseases often serving as the key point of contact for patient-centered and holistic care. [44]
Ireland	The national Rare Diseases Technology Review Committee (RDTRC) enables stakeholder input (clinicians and patients) in HTA by providing input on recommendations and/or guidelines to decision-makers. Established in 2018, the RDTRC reviews proposals for existing products for rare diseases, makes recommendations, and contributes to the development of clinical guidelines.[45]
Italy	In Italy, patients with rare diseases have multiple pathways to access orphan medicines. The primary route is through the European Medicines Agency's centralised authorisation procedure. If an orphan drug is not authorized, patients can access it through alternative procedures such as compassionate use or individual prescription. National legislation also supports patients' access to the best therapies available, including availability of orphan drugs. [46]

Country	Provisions and/or Policies at Country Level
Japan	In Japan, the Orphan Drug/Medical Device Designation System is overseen by the Minister of Health, Labour, and Welfare. Designation is based on the opinion of the Pharmaceutical Affairs and Food Sanitation Council (PAFSC), and specific criteria must be met for a product to be designated as an orphan. [47]
Korea	In Korea, a web-based repository system was developed for rare disease data, enabling easier access and organisation of information as well as the establishment of the Korean Rare Disease Knowledge Base to help foster research and knowledge of rare diseases in Korea with a focus on factors such as genetic variants, clinical directory for diagnosis and care, disease review and ongoing rare disease study.[48]
Philippines	In 2020, the Food and Drug Administration (FDA) worked on streamlined regulations for clinical trials, prioritising expedited approval for rare diseases and public health emergencies. The aim is to enhance the regulatory process, facilitate application evaluation, and improve access to investigational drug products for these specific health concerns.[49]
Poland	The Plan for Rare Diseases for 2021-2023 contains a list of 40 specific actions and timelines to improve medical care for patients with rare diseases. There are six core areas of the Plan that include defining guidelines, improving access to medicines, creating a registry of rare diseases, creating an information platform, setting criteria for the establishment of rare diseases centres of expertise, and introducing a rare disease patient passport. The plan also considered a series of priority legislative tasks. among others.[50]In 2021, the acting Health Minister announced that Poland would invest financially in efforts to address rare diseases, including the creation of centres of expertise, programs or projects to improve diagnosis of rare diseases and improved access to medicines and foods for special nutritional needs, to name a few.[51]
Singapore	Singapore has improved access to therapeutic products for individuals with rare diseases, supporting the import and supply of unregistered medications when necessary and as regulated by the Health Sciences Authority.
Sweden	Sweden is a member of the European Medicines Agency's Committee for Orphan Medicinal Products (COMP) that evaluates and recommends orphan designation for medicines targeting rare diseases.
Switzerland	The Swiss Registry for Rare Diseases (SRSK) collects epidemiological data and tracks changes in rare disease diagnosis. It enables patient participation in research, promotes data harmonisation, facilitates collaboration with international registries, and establishes a communication network. Switzerland also has a National Rare Disease Policy aim to improve health conditions and establish a health hardship commission.
Taiwan	The Rare Disease and Orphan Drug Act in Taiwan supports the development and availability of orphan drugs and special nutritional foods for rare diseases. Designated drugs can be considered for inclusion in the National Health Insurance Pharmaceutical Benefits and Reimbursement Scheme.
The Netherlands	A process broadens conditional marketing authorisation for drugs targeting rare diseases, enabling access with limited initial data. Additionally, collaborative arrangements with healthcare professionals evaluate and determine the inclusion of orphan drugs in the basic healthcare package. Patient access to advanced therapy medicinal products in the country is challenged related to the assessment pathway and willingness to pay.[52]
Turkey	The Social Security Institution (SGK) and the Turkish Medicines and Medical Devices Agency (TMMDA) oversee accessibility and licensing of orphan drugs. In accordance with the Regulation on Medicinal Products for Human Use purpose, the Ministry of Health completes a preliminary examination. Orphan drugs not approved by use for an indication and not licensed are delivered to a patient by using an early access procedure that allowed physicians to prescribe off-label medications.[53]Approved off-label drugs are imported with the help of the Turkish Pharmacists Association.
United Kingdom	NICE provides specialised guidance for very rare conditions with most defined by the National Institute for health Research Innovation Observatory (NICE).[54] The Highly Specialised Technologies Program within NICE reviews eligible drugs for rare diseases using a separate and independent advisory committee whose members are knowledgeable in rare diseases or disorders.[36]

Country	Provisions and/or Policies at Country Level
United States	The United States Food & Drug Administration (FDA) instituted a breakthrough therapy process expedites the review of innovative treatments with substantial improvements, fostering collaboration with the FDA and streamlined development. Additionally, the FDA Accelerated Approval Program enables the fast-track approval of drugs for serious conditions and address unmet medical need based on a surrogate endpoint.

HTA Recommendations

HTA recommendations for final funding decisions may be either non-binding (a negative recommendation does not necessary equate to a negative coverage decision) or binding (there is a legal obligation to consider the outcome of the HTA when deciding or determining coverage.) [5] In the context of the LC mapping of HTA mechanisms, systems and processes, the majority of countries (12) reported binding recommendations.

Table 5: HTA Recommendations: Binding or Non-Binding Status

Countries with binding HTA recommendations	Countries with non-binding HTA recommendations	Countries where status is unclear and/or unknown
Brazil, France, Germany, Israel, Italy, Korea, Philippines, Slovakia, Sweden, Switzerland, Taiwan, United Kingdom	Australia, China, Columbia, Denmark, Ireland, Poland, Singapore, The Netherlands	Argentina, Belgium, Canada, Japan, South Africa, Turkey, United States

Where established, HTA processes serve as a bridge to support the regulatory decision coverage and/or reimbursement decision making. [55]In some countries, and to increase efficiencies and accelerate timelines, parallel practices (concurrent regulatory and reimbursement reviews) have been introduced. Generally, the regulatory review process includes safety, quality, and efficacy while the HTA review addresses clinical and/or cost effectiveness, in addition to other relevant factors. The countries with parallel practices include **Australia, Brazil, Canada, France, Germany, Turkey,** and the **United Kingdom**.

In other countries, processes are either not parallel or lack clear definition. These countries include **Argentina, Belgium, China, Columbia, Denmark, Ireland, Israel, Italy, Japan, Philippines, Poland, Singapore, Slovakia, South Africa, Sweden, Switzerland, Taiwan, The Netherlands, South Korea,** and the **United States**.

Table 6: HTA Assessments and Negotiation of Drug Price

Countries with parallel practices	Countries with separate processes and/or unknown
Australia, Brazil, Canada, France, Germany, Turkey, United Kingdom	Argentina, Belgium, China, Columbia, Denmark, Ireland, Israel, Italy, Japan, Philippines, Poland, Singapore, Slovakia, South Africa, Sweden, Switzerland, Taiwan, The Netherlands, South Korea, United States

It is evident that in some countries, the reimbursement system can be comprehensive and complex.

- **Argentina** created the National HTA Commission (AGNET) to assess health technologies for reimbursement decisions using efficacy and efficiency standards. Argentina's reimbursement system is considered more comprehensive than many other countries in Latin America, with provisions to reimburse up to 70% of the value of some prescription drugs under social welfare schemes.[11]

- In **France**, pharmaceutical companies can set the prices for their authorised drugs, but reimbursement status and pricing

negotiations are separate processes. Reimbursement status is granted by the Transparency Commission, and pricing is negotiated with the Economic Committee for Health Products (CEPS). All pharmaceuticals, medical devices, and procedures must be assessed by the French National Authority for Health (HAS) before being included on the list of reimbursed products and services. The assessment is based on medical evidence, and regulated prices are determined based on the HAS opinion through a convention with CEPS. The reimbursement status and pricing are determined independently by separate bodies, CEPS and HAS.

Cost-effective analysis is an important element in HTA with a focus on the economic value of health gains by a new health technology. This is particularly relevant as HTA bodies or agencies provide recommendations on technologies for reimbursement by healthcare systems, particularly as establishing health technology prices too low may impact research and development by manufacturers and setting prices too high may limit patient access to the technology or drug.[3]

Table 7: Pricing and Reimbursement

HTA body is responsible for pricing and reimbursement	HTA body is not responsible for pricing and reimbursement
Israel, Italy, Singapore, Slovakia, Sweden, South Korea, Turkey	Argentina, Australia, Belgium, Brazil, Canada, China, Columbia, Denmark, France, Germany, Ireland, Japan, Philippines, Poland, South Africa, Switzerland, Taiwan, The Netherlands, United Kingdom, United States

According to a regulatory review of an HTA study in Asia, and examining regulatory versus HTA requirements, evidentiary requirements for clinical and economic evaluations may be classified in terms of population, clinical trial design, comparator, endpoint, and statistics. While these areas relate to regulators and HTA payers, the difference in stakeholder needs may lead to a lack of alignment, including the use of single-arm studies.[21]

Table 8: Regulatory Approval Processes

Countries with regulatory approval processes in place	Countries where it is unknown and/or information is not available for regulatory approval processes
Argentina, Australia, Belgium, Brazil, Canada, China, Colombia, Denmark, France, Germany, Israel, Italy, Japan, Philippines, Poland, Singapore, Slovakia, South Africa, Sweden, Switzerland, Taiwan, Netherlands, South Korea, Turkey, United Kingdom, United States	Ireland

Those countries that have implemented a process for concurrent HTA and regulatory reviews have predominantly well-established or mature HTA systems. There are several countries that have implemented practices or measures. For instance:

- **Belgium.** In Belgium, 'managed entry agreements' (MEAs) are used to address medical needs, provide patient access to new medicines, offer manufacturers market options, manage risks, and limit budget impact. MEAs are proposed by the commission for reimbursement of medicines (CRM) or manufacturers in response to negative reimbursement decisions or lack of a decision.

- **Philippines.** The HTA Process Guide involves the Price Negotiation Board (PNB) to assess the value of new health technologies for price negotiations. If a health technology is deemed unaffordable or lacks value for money, it is referred to the PNB for action. The PNB's assessment may take approximately four weeks, and final recommendations are withheld until cost issues are resolved. Additionally, safety, efficacy and product quality is evaluated by the Philippines Food and Drug Administration (FDA) whereas the HTA Council (HTAC) contextualises product use in the health system by evaluating clinical, economic, ethical, legal, social and health system impacts.[21]

- **Poland.** HTA assessments and drug price negotiations are conducted separately but sequentially. Specifically, after the AOTMiT

issues its recommendation, negotiations with the Economic Commission of the MoH are crucial for reaching a decision on reimbursement.

- **Switzerland.** The Federal Office for Public Health is the national authority responsible for the review and determination of price for every medicinal product reimbursed under health insurance in the country.[56]Switzerland has seen a rise in the number of drugs receiving rebates, especially in cancer treatment. These rebates were not limited to expensive drugs and varied greatly. However, many of these drugs were considered to have low clinical value, which could cause delays in determining prices and hinder access to the medications.

Conclusion

The HTA landscape is constantly evolving, with new technologies that improve patient outcomes showing great promise in treating cancers. In the lymphoma treatment landscape, new therapies and emerging biotherapeutic products are transforming cancer care and treatment. These advancements are occurring despite potential challenges as they progress through the pipeline including, for instance, economic or health system barriers.

As the scope of HTA mechanisms, systems and processes vary significantly, patient involvement in HTA to ensure the patients' perspective on the value of technologies is essential. It is important for patient organisations engaged in HTA processes at a country level to plan early and prepare which type of input they will provide during the HTA submission phase.

Although patients may be involved across the HTA continuum, there are challenge that some patient organisations face. Patient organisations, often resource constrained, are expected to collect, and incorporate evidence that best reflects their respective patient community, namely patient experiences, and unmet needs. This data is not usually readily available and there is an added cost in securing it in a validated, credible manner. Collection and analysis of data involves a unique skillset that may not be available in the local organisation. Additionally, patient organisations encounter limited and/or insufficient time allowance for involvement given the capacity, resources and expertise required for planning, preparedness, interpretation of data, and the development of HTA written submissions.

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