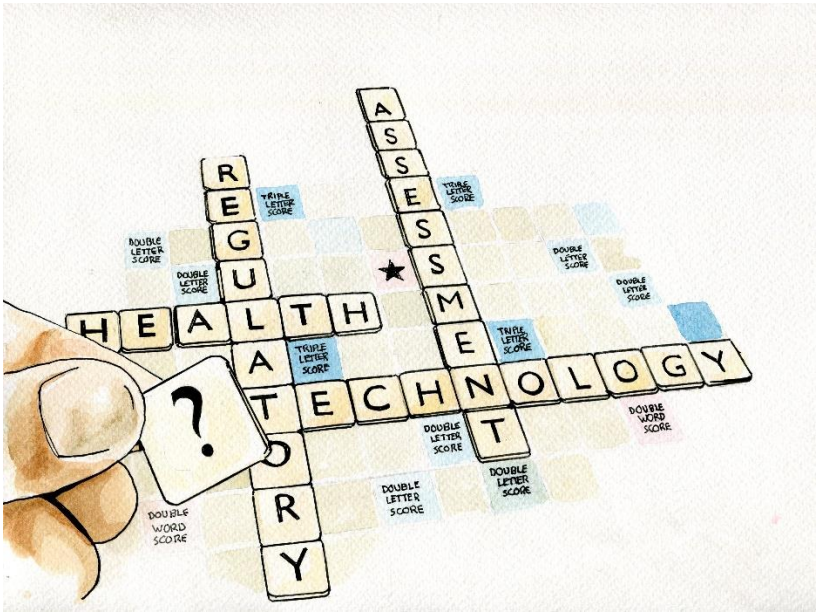

How has the pandemic accelerated the acceptance and utility of RWD/RWE in regulatory/HTA decision making?

9th-10th March 2022

Workshop Report

CIRS Centre for Innovation in Regulatory Science

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Report details

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About CIRS

The Centre for Innovation in Regulatory Science (CIRS) is a neutral, independent UK-based subsidiary of Clarivate plc. CIRS' mission is to maintain a leadership role in identifying and applying scientific principles for the purpose of advancing regulatory and Health Technology Assessment (HTA) policies and processes. CIRS provides an international forum for industry, regulators, HTA and other healthcare stakeholders to meet, debate and develop regulatory and reimbursement policy through the innovative application of regulatory science. It is governed and operated by Clarivate for the sole support of its members' activities. The organisation has its own dedicated management and advisory boards, and its funding is derived from membership dues, related activities and grants.

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Section 1: Executive Summary

Background to the workshop

This workshop builds on the outcomes of the CIRS Professor Breckenridge memorial workshop in December 2020, as well as the 2021 workshop on utilisation of digital technologies in clinical development.

The data landscape is changing due to the evolution of genomics, proteomics, imaging, clinical data and wearables. However, the use of such data in drug development is still maturing, as highlighted by the recent challenges and learnings of collecting data during the COVID-19 pandemic (for both COVID-19 and non-COVID-19 therapies).

Real-world data/evidence (RWD/RWE) can bring value to every stage of a drug's life cycle. Although regulatory and HTA submissions are likely to remain focused on randomised controlled trials (RCTs) in the future, these are also likely to be supplemented with RWD/RWE. As more technologically complex innovations are brought through development, there will be a need for early access routes that include robust ways of measuring these products' promise in the real world. With early access medicines it is important to ensure an ongoing benefit-risk assessment for the regulators and relative effectiveness assessment for the HTA agencies. Thus, the development and alignment between companies, HTA agencies, regulators and payers in the RWD/RWE space is critical. The focus needs to be on an agreement for continuous RWD analysis, not just for the reporting of adverse events.

Indeed, the discussion of post-licensing evidence generation early in development is becoming increasingly important, especially for conditional/early access medicines, where a life cycle approach is needed by both regulatory and HTA assessments. However, this will require regulatory agencies, HTA agencies and industry to come together to standardise datasets, data capture and analysis to ensure regulatory and HTA grade methodologies and data.

This workshop will focus on the changing RWD/RWE data landscape and lessons learned from the pandemic for early access medicines, such as how will RWD/RWE aid a life cycle approach to the assessment of medicines from a regulatory and HTA/payer perspective, as well as what are the challenges that companies and agencies face in ensuring that RWD/RWE is fit for purpose?

Workshop objectives

- Discuss the changing data landscape and provision of fit-for-purpose data for regulatory and HTA decision making, with a focus on use of RWD/RWE.
- Identify through case studies how RWD/RWE has or could be used to enable regulatory and reimbursement decisions through the life cycle of a medicine.
- Recommend stakeholder and collaborative activities to enable both alignment and utilisation of RWD/RWE by HTA agencies, regulators and payers for decision making during a medicine's life cycle.

Venue/format

The workshop was held virtually over two days (9th-10th March 2022).

Definitions

FDA defines RWD and RWE as follows:

- RWD are data relating to patient health status or the delivery of health care routinely collected from a variety of sources.
- RWE is the clinical evidence regarding the usage and potential benefits, or risks of a medical product derived from analysis of RWD.

Examples of RWD include data derived from electronic health records, medical claims data, data from product and disease registries, patient-generated data including from in-home use, and data gathered from other sources that can inform on health status, such as digital health technologies.

Source: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/real-world-data-assessing-electronic-health-records-and-medical-claims-data-support-regulatory

Workshop Programme

Please note, affiliations are stated as they were at the time of the meeting (9th-10th March 2022).

Session 1: Early access of COVID-19 vaccines and therapeutics – what role did RWD/RWE play in enabling regulatory and HTA decision making?	
CIRS welcome and introduction	**Dr Neil McAuslane,** *Director, CIRS*
Session Chair introduction	**Adj Prof John Skerritt,** *Deputy Secretary for Health Products Regulation, Department of Health, Australia*
What role did RWE play in enabling the early deployment of COVID-19 vaccines and therapeutics and what lessons have been learned?	
Company perspective **Regulatory perspective**	**Deepa Malhotra**, *Head of RWD for vaccines, Pfizer, USA* **Dr Peter Arlett,** *Head of Data Analytics and Methods Taskforce, European Medicines Agency (EMA)*
COVID-19 treatments and vaccines - International Coalition of Medicines Regulatory Authorities (ICMRA) perspective on clinical trial efficacy vs RWE effectiveness	**Dr Celia Lourenco**, *Director General, Biologic and Radiopharmaceutical Drugs Directorate, Health Canada*
Has HTA been used for COVID-19 treatments and if not how will the transition to an HTA process work for these treatments?	**Dr Nick Crabb,** *Programme Director, Scientific Affairs, National Institute of Health and Care Excellence (NICE), UK*
Session 2: RWE for decision making: what are today's opportunities?	
Session Chair introduction	**Lorraine Nolan**, *CEO, Health Products Regulatory Authority (HPRA), Ireland*
RWE for decision making: what are opportunities for today and in the future?	
Regulatory perspective **Payer perspective** **Company perspective**	**Dr John Concato,** *Associate Director for RWE, Office of Medical Policy, Center for Drug Evaluation and Research (CDER), Food and Drug Administration (FDA), USA* **Jo de Cock,** *Former CEO, National Institute for Health and Disability Insurance, Belgium* **Prof Thomas Kuhler,** *Head of Global Regulatory Science and Policy for EU/AMEE, Sanofi*
Regulatory acceptance and use of RWE generated within and from other jurisdictions – what are the challenges and how are agencies adapting?	
Latin American regulatory perspective **Asian regulatory perspective**	**Gustavo Mendes Lima Santos,** *General Office of Medicines and Biological Products (GGMED), ANVISA, Brazil* **Junko Sato,** *Office Director, Office of International Program, Pharmaceutical and Medical Devices Agency (PMDA), Japan*

Session 3: RWE acceptance by regulatory and HTA agencies for early access medicines: How can this be best achieved and what are the key challenges?	
Session Chair introduction	**Dr Nicole Mittmann**, *Chief Scientific Advisor and Vice President, Canadian Agency for Drugs and Technologies in Health (CADTH)*
Acceptance of RWD as a trustworthy source of evidence for early access medicines – what are the key challenges to increase the utility of RWE for regulatory and HTA decision making?	**Dr Harald Enzmann,** *Chair, EMA Committee for Medicinal Products for Human Use (CHMP)*
Aligning regulatory and HTA RWE needs, pre- and post-approval to avoid duplication – what are the challenges and how could this be best achieved?	**Dr Anja Schiel,** *Lead Methodologist/ Statistician/Team leader for international HTA, Norwegian Medicines Agency*
Would an international roadmap for use of RWE in decision making be of value?	
Regulatory perspective	**Dr Melissa Kampman,** *Manager and Senior Epidemiologist, Marketed Health Products Directorate, Health Canada*
Company perspective	**Bart Barefoot,** *Director, RWE Policy and Advocacy, GlaxoSmithKline, UK*
Session 4: Life cycle approaches for regulatory, HTA and payer decision making on early access medicines – what is the role of RWE?	
Session Chair introduction	**Dr Tomas Salmonson,** *Consultant, Consilium Salmonson & Hemmings, Sweden*
What is the value of RWE from the patient perspective and how should this be factored into decision making?	**Francois Houyez,** *Treatment Information and Access Director / Health Policy Advisor, EURORDIS*
Panel discussion Each panellist had eight minutes to provide their thoughts on the future utilisation of RWE as part of a life cycle approach to development, review and reimbursement. **Patient perspective – Valentina Strammiello,** *Head of Programmes, European Patients Forum, Belgium* **Company perspective** – **Adrian Griffin,** *Vice President for HTA & Reimbursement Policy, Johnson & Johnson, UK* **Regulatory perspective** – **Dr Claus Bolte,** *Head of Sector Marketing Authorisation, Swissmedic* **HTA perspective** - **Andrew Mitchell**, *Strategic Adviser, Evaluation, Australian Government Department of Health* **Payer perspective – Dr Daniel Erdmann,** *Team Lead, GKV-Spitzenverband, Germany*	

Session 5: Breakout discussions	
Session Chair introduction	**Dr Brian O'Rourke,** *Chair, CIRS HTA Steering Committee*
Breakout A: How could RWE shape a more predictive process of "efficacy to effectiveness assessment"?	**Chair: Niklas Hedberg,** *Chief Pharmacist, Dental and Pharmaceuticals Benefits Agency (TLV), Sweden* **Rapporteur: Sang Mi Lee,** *Access Lead, Personalized Healthcare, CGP and Tumour Agnostic Portfolio, F.Hoffmann-La Roche, Canada*
Breakout B: Early access medicines: optimising the use of RWE for regulatory and HTA decision making – what are the opportunities, barriers and solutions?	**Chair: Prof Hubert Leufkens,** *Emeritus Professor, Utrecht University, The Netherlands* **Rapporteur: Rob Kalesnik-Orszulak,** *Director, Regulatory Innovation Lead for RWE and Data Science, Bristol Myers Squibb, USA*
Breakout C: Aligning RWD/E to meet regulatory and HTA needs within and across jurisdictions – how can this be best achieved?	**Chair: Prof Anthonius de Boer,** *Chairman of the Medicines Evaluation Board, The Netherlands* **Rapporteur: Dr Stephanie Manson,** *Senior Director, Worldwide Value and Access, Novartis, USA*
Breakout D: What framework or criteria need to be in place to ensure fit-for-purpose RWE for utilisation as part of a life cycle approach for medicines assessment by HTA and regulatory agencies?	**Chair: Dr Álmath Spooner,** *Director, Regulatory Policy and Intelligence, AbbVie, Ireland* **Rapporteur: Lucia D'Apote,** *Director, ELMAC Lead for Global Regulatory and R&D Policy, Amgen, UK*

Key points from presentations

Please note that the following presentation summaries represent the views of the individual presenter and do not necessarily represent the position of the organisation with which they are affiliated. Affiliations are stated as they were at the time of the meeting (9th-10th March 2022).

Session 1: Early access of COVID-19 vaccines and therapeutics – what role did RWD/RWE play in enabling regulatory and HTA decision making?

Deepa Malhotra, *Head of RWD for Vaccines, Pfizer, USA*, gave a company perspective on the role that RWE played in the deployment of COVID-19 vaccines and therapeutics. The COVID-19 pandemic demonstrated that RWE is equipped to rapidly generate and disseminate high quality evidence from existing and novel data sources. Decision makers, including regulators, legislators and the medical community, have learned to utilise insights and acknowledge value derived from RWE. The future goal should be to leverage and accelerate use of RWD to generate RWE earlier, and more efficiently for key decisions, regulatory or otherwise.

Dr Peter Arlett, *Head of Data Analytics and Methods Taskforce, European Medicines Agency (EMA),* gave a regulatory agency perspective on the role that RWE played in the deployment of COVID-19 vaccines and therapeutics. The pandemic highlighted the need to invest in RWE as well as enabling large, high quality clinical trials. The mobilisation of RWE during the pandemic gave key learnings around proactivity, data quality issues, establishing methods and expert regulatory assessment. There has been major progress - catalysed by the pandemic - on EMA big data priority recommendations, and new legislation from March 2022 has given the agency a mandate to strengthen the place of RWE.

Dr Celia Lourenco, *Director General, Biologic and Radiopharmaceutical Drugs Directorate, Health Canada,* and *Co-Chair of the International Coalition of Medicines Regulatory Authorities (ICMRA) COVID-19 working group,* spoke about learnings from the COVID-19 pandemic in terms of clinical trial efficacy vs RWE effectiveness. The pandemic resulted in unprecedented levels of data and information, which included numerous clinical studies that were often single site with small sample sizes. Moving forward, it will be important to focus on well-designed clinical trials and observational studies to support decision making through international collaboration. As well as continuing to be a venue convening regulators in crisis management, ICMRA is initiating a project to develop standard clinical trial protocols that can be deployed quickly in future pandemics.

Dr Nick Crabb, *Programme Director, Scientific Affairs, National Institute for Health and Care Excellence (NICE), UK,* gave an overview of NICE's activities during the COVID-19 pandemic, which included co-ordinating the Research to Access Pathway for Investigational Drugs for COVID-19 (RAPID-C19) programme, producing COVID-19 guidelines, developing early economic models and facilitating international collaboration. Going forward, HTA agencies should explore a life cycle approach to COVID-19 assessments and must accept limited and disparate randomised controlled trial (RCT) evidence during a pandemic of a new disease. RWE may be the best evidence available and should be used to inform initial assessments, while emergent RWE can inform rapid updates.

Session 2: RWE for decision making: what are today's opportunities?

Dr John Concato, *Associate Director for Real-World Evidence Analytics, Office of Medical Policy, Centre for Drug Evaluation and Research (CDER), US Food and Drug Administration (FDA)*, gave an overview of FDA's RWE Programme that is focused on the implementation of RWE through internal processes, external stakeholder engagement, demonstration projects and guidance development. Looking forward, it is important to recognise that all data sources and study designs have strengths and limitations. Other study designs can supplement—but not replace—traditional clinical trials for regulatory decision making. Clear and consistent use of terminology can advance understanding and ongoing collaborative efforts can help to identify factors that promote generation of robust RWE.

Jo de Cock, *Former CEO, National Institute for Health and Disability Insurance (NIHDI), Belgium***,** spoke about how payers are increasingly interested in RWE yet remain cautious about its use. Ongoing structured and iterative dialogue among stakeholders along the product life cycle should be developed further. There is a need to move away from fragmented recommendations to comprehensive guidance and improvement of standards of RWD studies. Practical learnings must be shared to support decision makers; this could be facilitated through a learning network.

Junko Sato, *Office Director, Office of International Program, Pharmaceutical and Medical Devices Agency (PMDA), Japan,* gave an overview of PMDA's experience in using RWE in regulatory decisions. PMDA has longstanding experience in using RWE and is evolving its use through consultation on registry utilisation for applications; implementation of new guidelines on product development utilising RWD; and establishing a working group on RWD. RWE can only contribute to regulatory decision making when both reliable RWD and appropriate analyses are used. Experience sharing and multi-stakeholder collaboration are essential to accelerating the utilisation of RWD.

Gustavo Mendes Lima Santos, *General Office of Medicines and Biological Products (GGMED), Brazilian Health Regulatory Agency (ANVISA)***,** spoke about ANVISA's experience in using RWE in regulatory decisions. Challenges include issues around data quality, data validation and patient registries. Transparency can be a problem with observational and pharmacovigilance studies; there must be regulatory procedures to prevent excessive analyses to generate the result wanted. In Brazil, there is a need to standardise the terms and rules for RWD use and evaluation; this must involve collective work between regulators, industry, agencies and academia.

Session 3: RWE acceptance by regulatory and HTA agencies for early access medicines: How can this be best achieved and what are the key challenges?

Dr Harald Enzmann, *Chair, Committee for Medicinal Products for Human Use (CHMP), European Medicines Agency (EMA)* described how the COVID-19 pandemic has demonstrated the utility of RWD for regulatory decision making and the feasibility of large, fast RCTs. While RWD is widely accepted for safety, there are challenges in its use for efficacy, such as confounding factors and alignment with other stakeholders. Pushing for a guideline on the use of RWD now may be premature and may cement a conservative view among regulators. Therefore, going forward, it may be better to probe the regulatory system with well-prepared cases of RWD that may facilitate acceptance (though not preference over RCTs).

Dr Anja Schiel, *Lead Methodologist/Statistician/Team leader for international HTA, Norwegian Medicines Agency,* spoke about the challenges and potential solutions to aligning regulatory and HTA RWE needs. It is essential to recognise that the decision frameworks and underlying questions of regulators and HTA agencies are fundamentally different. Decisions on when, what and how to collect data need to be taken early enough, collaboratively and should respect and reflect the needs of different decision frameworks;

effective communication is key to ensuring this. The overall aim of data collection should be to reduce uncertainty in decision making for all stakeholders.

Dr Melissa Kampman, *Manager and Senior Epidemiologist, Marketed Health Products Directorate, Health Canada,* gave an overview of Health Canada's efforts to strengthen the use of RWE for drugs in Canada. The agency is committed to domestic and international collaborations to align the use of RWD/E across the product life cycle and jurisdictions. Attention must be paid to existing activities in the RWD/E space to avoid duplication and determine the best path forward towards convergence, harmonisation and/or the development of a common roadmap.

Bart Barefoot, *Director, RWE Policy & Advocacy, GlaxoSmithKline,* spoke about the value that international roadmap(s) for use of RWE in decision making would have to all stakeholders. However, different decision-making contexts e.g. regulatory vs HTA, may require distinct but linked roadmap destinations. To make progress towards an international RWE roadmap, three development principles must be followed: build on experience and knowledge already gained, build with modular blocks and build together iteratively. These principles should be underpinned by cross-stakeholder partnerships and collaboration.

Session 4: Life cycle approaches for regulatory, HTA and payer decision making on early access medicines – what is the role of RWE?

François Houÿez, *Director of Treatment, Information and Access, Eurordis,* gave a patient group perspective on the value of routine practice data or RWD. While RWD holds promise for R&D, there are many outstanding questions around the conclusiveness and robustness of RWD compared to trial data. These include who should pay for RWD; who should have access to RWD; are patients informed when RWD are used; and whether RWD should be a public good. As healthcare systems are not well equipped to input data to a high standard, patients could instead play a role in gathering RWD by using mobile sensors/digital devices.

Panel discussion - Panellists representing industry, regulatory agencies, HTA agencies, payers and patients were asked to provide their thoughts on the future utilisation of RWE as part of a life cycle approach to development, review and reimbursement. A graphical summary of key points from this discussion can be found on the following page, with further detail provided on p48-49.

Summary of panel discussions

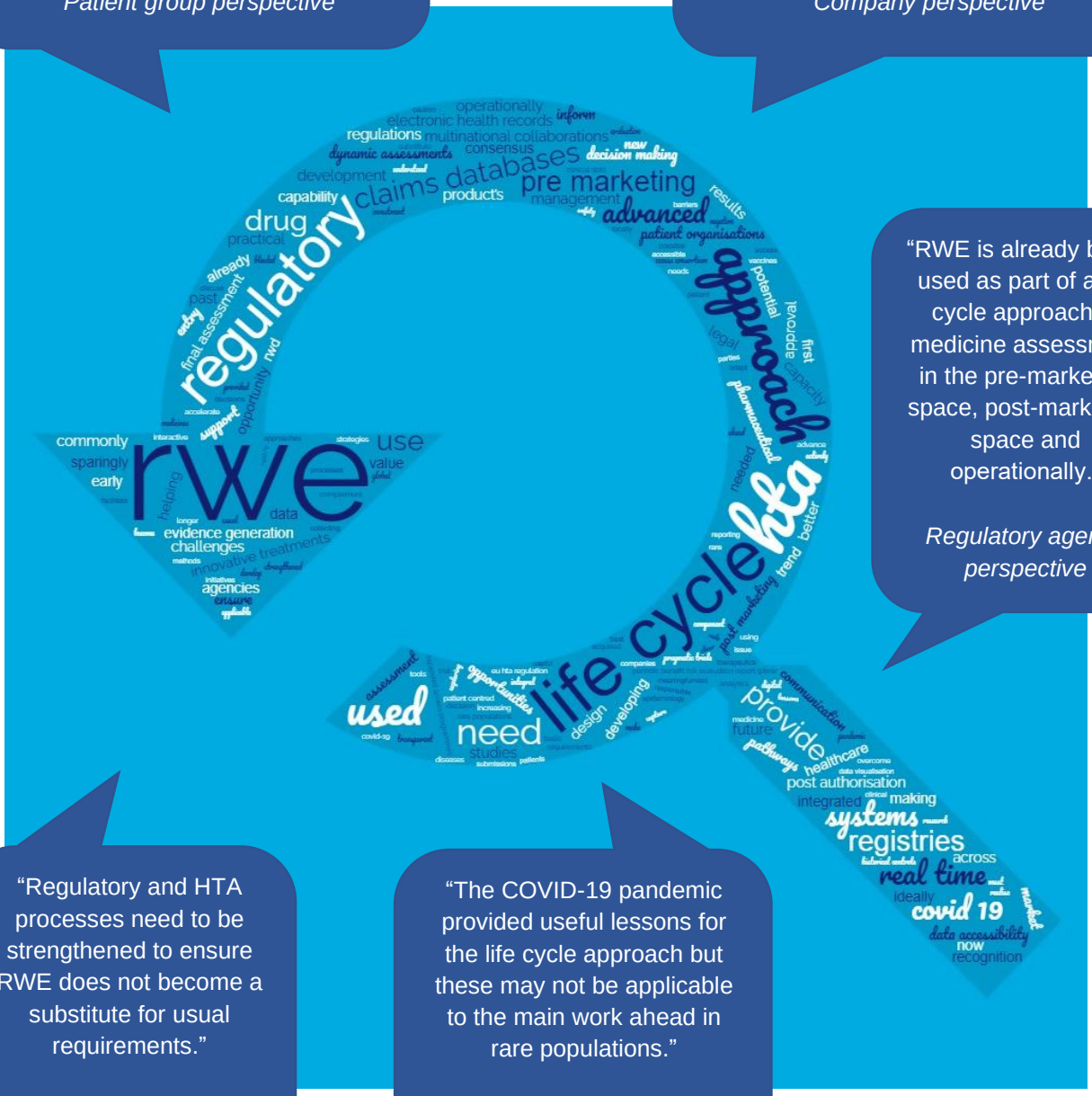
Stakeholder reflections on the future utilisation of RWE as part of a life cycle approach to development, review and reimbursement

"The role of patient organisations in collecting RWE should be given more recognition and investment to overcome capacity and capability barriers."

Patient group perspective

"The future of RWE lies in real time evaluation and decision making, with opportunities in new regulatory and HTA pathways, the EU HTA Regulation and advanced tools/analytics."

Company perspective



"RWE is already being used as part of a life cycle approach to medicine assessment in the pre-marketing space, post-marketing space and operationally."

Regulatory agency perspective

"Regulatory and HTA processes need to be strengthened to ensure RWE does not become a substitute for usual requirements."

Payer perspective

"The COVID-19 pandemic provided useful lessons for the life cycle approach but these may not be applicable to the main work ahead in rare populations."

HTA agency perspective

Breakout discussions

A) How could RWE shape a more predictive process of "efficacy to effectiveness assessment"?

This breakout group concluded that RWE already has a role in addressing the efficacy-effectiveness gap but is not being used in a predictive process. Challenges that were identified related to accessing high quality data in a timely manner; trust; and responsibility of risk/investment. Potential policy solutions could be greater transparency and openness on data access and data sharing; developing guidance on what constitutes good RWE; and a platform for open dialogue between stakeholders so that research questions can be developed together.

Recommendations for CIRS and/or other groups:

1. Develop guideposts/standards around focused RWE use cases e.g. how to address the efficacy-effectiveness gap in a specific therapeutic area or situation.

B) Early access medicines: optimising the use of RWE for regulatory and HTA decision making – what are the opportunities, barriers and solutions?

This breakout group concluded that there were two main opportunities for incorporating RWD/RWE into decision making for early access medicines: pre-approval, using RWE as external/hybrid controls to speed up development and shorten time to regulatory/HTA/payer approval; and post-approval, where RWE from registries, pharmacovigilance etc can facilitate better understanding of the medicine. Challenges that were identified included differences in stakeholder expectations; issues around data relevance and reliability; and gaps in expertise/mindset. The breakout group emphasised the need for all stakeholders to work together to overcome these challenges and implement solutions, such as the development of data standards and staff training to build competence in reviewing RWE.

Recommendations for CIRS and/or other groups:

1. Further cross-discipline workshops
2. Corresponding research projects e.g.
    a. Assessing different data standards in terms of strengths and limitations
    b. Evaluating when and where RWE approaches have been utilised successfully and unsuccessfully – this will help to set stakeholder expectations.

C) Aligning RWD/E to meet regulatory and HTA needs within and across jurisdictions – how can this be best achieved?

This breakout group identified key initiatives promoting RWD/E alignment, including the IMI Get Real Institute, regulatory information sharing through ICMRA, DARWIN-EU and the EU HTA Regulation. The group concluded that many initiatives are providing guidelines, addressing data quality and transparency, however, there are questions around who the audience is, whether the outputs are reaching decision makers and whether these initiatives are having an impact on the quality of individual drug evaluations. To enable stakeholder consensus on RWE acceptability, several policy changes may be required such as better pre-alignment on regulatory/HTA expectations, creating incentives for better quality RWE and ensuring that research questions are tailored to data capability.

Recommendations for CIRS and/or other groups:

1. More opportunities for regulators/HTA agencies/industry to work together, not only on RWE principles but also specific applications
2. Learn and share from best practice examples of RWE application.

D) What framework or criteria need to be in place to ensure fit-for-purpose RWE for utilisation as part of a life cycle approach for medicines assessment by HTA and regulatory agencies?

This breakout group agreed that the main advantages of a life cycle approach are timely patient access to innovative treatments as well as effective use of accelerated pathways and conditional marketing authorisation. Use of a life cycle approach also gives opportunities for a learning healthcare system, multi-stakeholder alignment and early dialogue. The breakout group concluded that the key building blocks of a life cycle approach framework are stakeholder engagement across the life cycle; integration of the patient perspective; legal clarification on data ownership; use of patient registries; data and digital policy infrastructure; comprehensive aligned/convergent guidelines; and consolidated use of tools post marketing.

Recommendations for CIRS and/or other groups:

1. Connect efforts from current multi-stakeholder initiatives
2. Engage on EMA regulatory science research needs
3. Establish a process to grade uncertainty.

Section 2: Presentations

Please note that the following presentation summaries represent the views of the individual presenter and do not necessarily represent the position of the organisation with which they are affiliated.

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Affiliations are stated as they were at the time of the meeting (9th-10th March 2022).

Session 1: Early access for COVID-19 vaccines and therapeutics – what role did RWD/RWE play in enabling regulatory and HTA decision making?

What role did RWE play in enabling the early deployment of COVID-19 vaccines and therapeutics and what lessons have been learned?

Company perspective

Deepa Malhotra, *Head of RWD for Vaccines, Pfizer, USA*

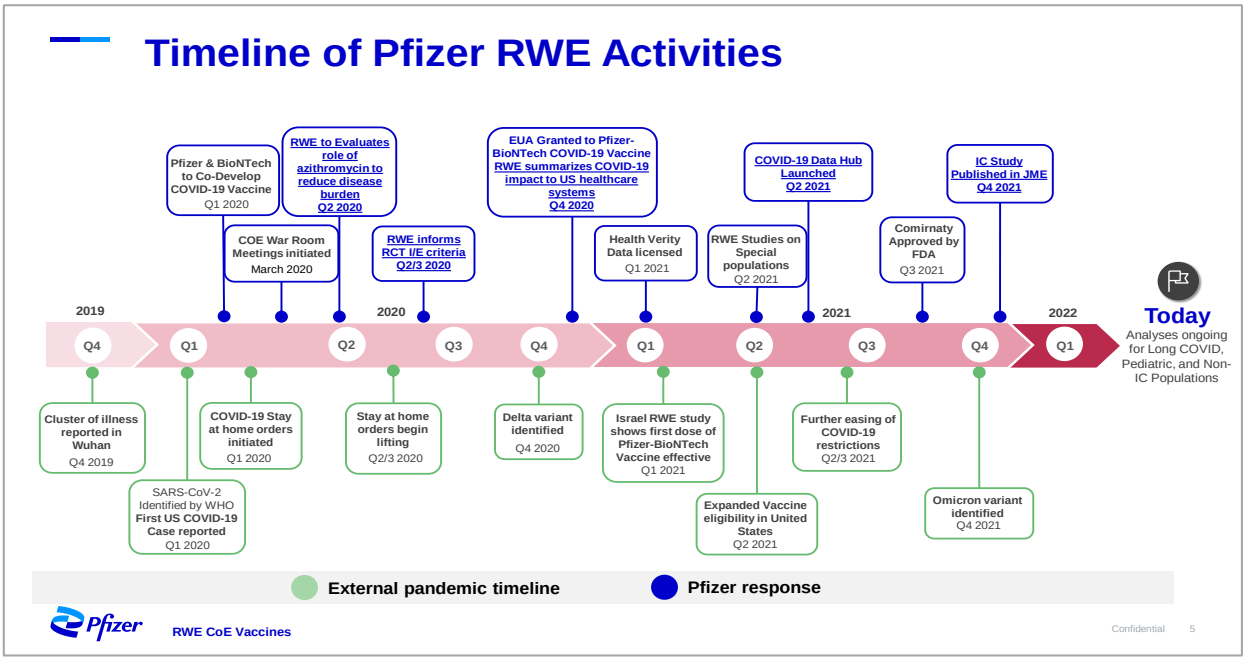
At the start of the COVID-19 pandemic, there were several challenges relating to RWD such as lack of literature on COVID-19, absence of COVID-19 RWD sources, limited data transfer infrastructure between hospitals and public health officials, inability to deliver real-time data and the need to modify existing surveillance systems to track COVID-19. In addition, there were numerous clinical challenges including limited understanding of the disease severity and at-risk populations, increasing burden on healthcare systems and varying reports of treatment effectiveness e.g. hydroxychloroquine.

In response to the enormous need for data, stakeholders globally came together to make public whatever data they could. However, this data needed to be verified to ensure that it was reliable and fit for purpose. As data sources rapidly increased over time, companies had to develop dynamic internal dashboards to keep up with the evolving data as well as the changing evidence needs with each wave of the pandemic.

Pfizer RWE activities in accelerated timelines

In March 2020, Pfizer decided to co-develop a COVID-19 vaccine in collaboration with BioNTech (see timeline on following page). RWE had a key role in determining the inclusion/exclusion criteria for the clinical trial and in answering frequent questions from internal and external stakeholders. The vaccine received Emergency Use Authorisation (EUA) from the FDA in Q4 2020, after an unprecedented nine months of development compared to previous timelines of up to 13 years. Key to this success was the range of stakeholders who came together to collaborate, exchange information and share decisions.

In Q2 2021, Pfizer began RWD studies for special populations that had not been included in the randomised controlled trials, such as immunocompromised populations, pregnant women and paediatric groups. The resulting RWE informed not only internal decisions within Pfizer, but also external regulatory authorities. By March 2022, Pfizer's RWD focus had shifted to long COVID-19, broader paediatric populations and emerging COVID-19 variants.



Acceptance of RWD

Pfizer has experience of several drug approvals based on RWE, which demonstrates the acceptance of RWD by regulators. For example, FDA approved a new use of transplant drug tacrolimus based on a non-interventional study providing RWE on effectiveness, which reflects how a "well-designed non-interventional study relying on fit-for-purpose RWD, when compared with a suitable control, can be considered adequate and well-controlled under FDA regulations" [1]. US legislators have also demonstrated their acceptance of RWD through the introduction of Bill S.1508, which provides for the use of emergency use authorisation data and RWE gathered during an emergency to support pre-market application for a formal approval.

Summary

RWE is equipped to rapidly generate and disseminate high quality evidence from existing and novel data sources. The COVID-19 pandemic has required decision makers, including regulators, legislators and the medical community, to utilise insights and acknowledge value derived from RWE. The future goal should be to leverage and accelerate use of RWD to generate RWE earlier, and more efficiently for key decisions, regulatory or otherwise.

References

[1] US Food and Drug Administration. FDA approves new use of transplant drug based on real-world evidence [online]. Published 16th July 2021. Accessed 1st July 2022 from: https://www.fda.gov/drugs/news-events-human-drugs/fda-approves-new-use-transplant-drug-based-real-world-evidence

What role did RWE have in enabling the early deployment of COVID-19 vaccines and therapeutics and what lessons have been learned?

Regulatory agency perspective

Dr Peter Arlett, *Head of Data Analytics and Methods Taskforce, European Medicines Agency (EMA)*

The vision of the European Medicines Regulatory Network is that by 2025, RWE use will have been enabled and its value established across the spectrum of regulatory use cases [1]. To progress this vision, in 2020 the Heads of Medicines Agencies (HMA)-EMA Joint Big Data Taskforce published ten priority recommendations focused on: establishing the Data Analysis and Real-World Interrogation Network (DARWIN-EU); data quality; data discoverability; skills; processes; analytics capability; delivery of expert advice; governance frameworks; international collaboration; and stakeholder engagement.

Back to basics

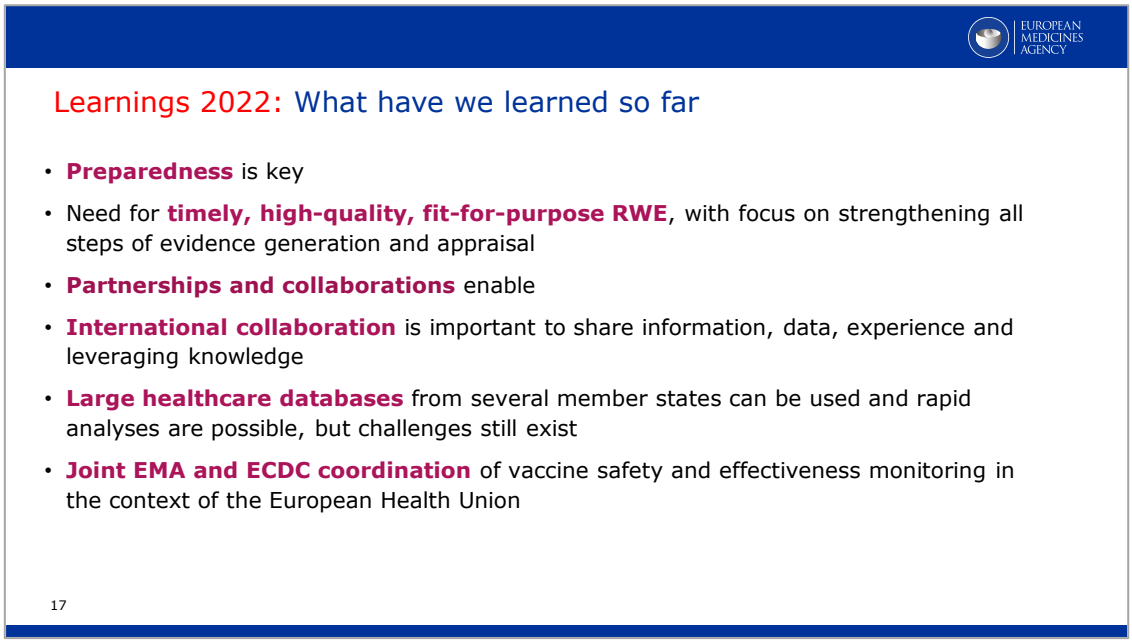
In March 2020, eight weeks after the publication of these recommendations, COVID-19 became the main concern for regulators around the world. Regulators were forced back to basics, playing the fundamental role of protecting public health by facilitating development and access to medicines, evaluating applications for marketing authorisations, monitoring the safety of medicines across their life cycle and providing information on medicines to healthcare professionals and patients.

RWE in the EMA response to COVID-19

In response to COVID-19, the EMA undertook several activities that involved RWE, including reviewing study results and promoting use of the EU post-authorisation studies register to support transparency, collaboration and good quality studies. In addition to initiating and funding projects, the EMA collaborated internationally through the International Coalition of Medicines Regulatory Authorities (ICMRA) and helped to strengthen the methodologies work of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance.

The ACCESS (vACcine Covid-19 monitoring readinESS) project led by Utrecht University and funded by EMA, was key to preparing for vaccine roll out. The project identified the required data sources, calculated background rates of adverse events of special interest, put in place study protocol templates and conducted feasibility analyses. This led to follow-on studies monitoring safety of the first vaccines and then later vaccine effectiveness studies, which marked a major evolution in roles as it was the first time a regulator at the European level had initiated and directly funded a vaccine effectiveness study.

There have been several learnings from the COVID-19 pandemic on the importance of timely, high-quality, fit-for-purpose RWE (see following page). Early considerations for pharmacoepidemiological analyses highlighted the need for caution when using observational studies for the primary demonstration of efficacy [2]. The pandemic showed that large healthcare databases from several member states can be used for real-time reporting and that rapid analyses are possible; however, challenges still exist, such as lags in data availability and variation in clinical practices.



Where are we now?

Despite the COVID-19 pandemic, there has been significant progress on implementing the HMA-EMA Joint Big Data Taskforce recommendations. The DARWIN-EU coordination centre has been selected, an advisory group established and planning is underway for a pilot to explore the potential for the European Health Data Space. A multi-stakeholder workshop on data quality was held in late 2021, with another planned for April 2022.

In addition to DARWIN-EU, the EMA is delivering RWE into decision making through the use of in-house accessible databases and studies procured through EMA framework contracts. 98 in-house analyses or studies have been performed since 2013, which have supported evidence needs of EMA Committees, particularly the Pharmacovigilance Risk Assessment Committee. Framework contracts have allowed access to 59 data sources in 21 EU countries, covering over 350 million people.

Six months into the pandemic, the European Commission published a legal proposal to expand EMA's mandate to act in preparation for and during public health emergencies. This legislation was adopted into law and became applicable in March 2022. This now means that the EMA must ensure access to RWD analysis to support crisis preparedness and response and must collaborate with the European Centre for Disease Control (ECDC) to establish a vaccine monitoring platform.

Summary

EMA's vision is that by 2025, RWE use will be enabled and value established across regulatory use cases. The COVID-19 pandemic has highlighted the need to invest in RWE as well as enabling large, high quality clinical trials. The mobilisation of RWE during the pandemic gave key learnings around proactivity, data quality, establishing methods and expert regulatory assessment. There has been major progress - catalysed by the pandemic - on big data priority recommendations, and new legislation from March 2022 has given the EMA a mandate to strengthen the place of RWE in regulatory decision making.

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COVID-19 treatments and vaccines: clinical trial efficacy vs RWE effectiveness

International Coalition of Medicines Regulatory Authorities (ICMRA) perspective

Dr Celia Lourenco, *Director General, Biologic and Radiopharmaceutical Drugs Directorate, Health Canada,* and *Co-Chair of the ICMRA COVID-19 working group*

ICMRA is an international coalition of key medicines regulators from every region of the world. It provides a global architecture to support enhanced communication, information sharing, crisis response and address regulatory science issues. ICMRA has 22 members, 14 associate members, and one observer, the World Health Organisation (WHO).

ICMRA activities during the pandemic

ICMRA has been very active during the pandemic, convening biweekly COVID-19 policy teleconferences co-chaired by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA), which have now become monthly. These meetings are supporting by the ICMRA COVID-19 working group and have discussed various subjects, such as emergency regulatory procedures, agilities implemented by regulators and considerations for remote inspections. Workshops were also held to dig deeper into key topics, such as data requirements for early clinical trials for vaccines and treatments, requirements for confirmatory trials, approaches for observational studies and the collection of RWD.

The ICMRA COVID-19 working group assisted with the development of several ICMRA statements, key of which was the statement calling on all stakeholders to design and conduct robust trials that support regulatory decision making. ICMRA also issued statements to promote confidence in COVID-19 vaccines and highlight the need for continued focus on developing COVID-19 therapeutics, in addition to vaccines.

Clinical trials vs RWE

Clinical trials and RWD/RWE are complementary and should both be part of the development continuum. Even at the preclinical stage RWE can be acquired, for example, for natural history studies, or to assess the standard of care and unmet needs resulting from current therapies. During clinical trials, RWE can be used when a control arm is not ethical or feasible and can be obtained from patient-reported outcomes. While Phase 4 studies are key to addressing outstanding questions about efficacy or safety, or to do head-to-head comparisons, RWE can also be used in observational studies to confirm effectiveness, support extension of indications and aid pharmacovigilance.

RWE case studies from the pandemic

Vaxzevria

The initial authorisations in the UK and EU for COVID-19 vaccine Vaxzevria were based on clinical trials with limited enrolment of individuals aged 65 and older. However, because of ethical considerations around how COVID-19 impacts older individuals more severely, in addition to supply limitations, Vaxzevria was rolled out to older individuals first. This led to large amounts of data accumulating quickly, which confirmed the effectiveness of the vaccine in the 65+ age group and were used to support subsequent authorisations in countries. Following publication of the RWE studies, the efficacy of Vaxzevria in older populations was confirmed with a Phase 3 trial that enrolled sufficient numbers of individuals in the 65+ age group to assess the efficacy and safety of the vaccine across all adult populations.

Hydroxychloroquine

Early in the pandemic, hydroxychloroquine was put forward as a potential drug for the treatment of COVID-19 based on findings from observational studies. However, the multinational WHO Solidarity trial demonstrated hydroxychloroquine's lack of efficacy on overall mortality, initiation of ventilation and duration of hospital stay. Reviews of the initial observational studies highlighted several issues including immortal time bias, selection bias and information bias [1]. While observational studies are helpful in demonstrating how a drug performs in a real-world setting, it is important to carefully design and analyse such studies to draw meaningful conclusions for clinical and regulatory decision making.

Summary

The COVID-19 pandemic resulted in unprecedented levels of data and information, which included numerous clinical studies that were often single site with small sample sizes. Moving forward, it will be important to focus on well-designed clinical trials and observational studies to support decision making. International collaboration will be increasingly important to achieve this goal by clarifying regulatory expectations at a global level and support rapid responses that will engender public confidence. As well as continuing to be a venue convening regulators in crisis management, ICMRA is initiating a project to develop standard clinical trial protocols that can be deployed quickly in future pandemics. As part of this work, it will be important to also look at developing criteria to avoid pitfalls in the design of observational studies.

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Has HTA been used for COVID-19 treatments and if not, how will the transition to an HTA process work for these treatments?

Dr Nick Crabb, *Programme Director, Scientific Affairs, National Institute for Health and Care Excellence (NICE), UK*

NICE activities during the pandemic

RAPID C-19

The Research to Access Pathway for Investigational Drugs for COVID-19 (RAPID C-19) is a multi-agency initiative that was established in April 2020 to enable rapid patient access to effective treatments for COVID-19 when there is evidence of benefit. It includes senior representatives from organisations with a key role in the UK development to access pathway, such as the National Institute for Health Research (NIHR), the Medicines and Healthcare products Regulatory Agency (MHRA), NICE and NHS England & Improvement. The NICE RAPID-C19 team is responsible for leading the development and co-ordination of the RAPID-C19 programme; providing secretariat function, horizon scanning and evidence synthesis; and preparing briefings for the Chief Medical Officer.

COVID-19 guidelines

In parallel with the RAPID C-19, but with close alignment, NICE guidelines centres developed COVID-19 guidelines. Recommendations in the guidelines were developed by a NICE Expert Advisor Panel, informed by evidence review. Where possible, NICE guidance informed NHS England Interim Policies on access to COVID-19 therapies, but sometimes differing timescales made this challenging.

Economic modelling

NICE supported initial procurement activities through the development of early economic modelling. For example, models to provide early indicative value signals were developed for remdesivir and neutralising monoclonal antibodies. Given the lack of mature information available, the results from these models did not constitute NICE guidance in the normal way but were an important contribution to decision making in a very difficult situation.

International collaboration

At the start of the pandemic, NICE initiated regular meetings with HTA colleagues in Scotland, Wales, Canada and Australia to share experiences and plans for COVID-19 work, particularly in the areas of RWE, HTA and economic modelling. The benefits of the meetings included understanding how others were responding to the pandemic and external HTA input into NICE's work. The agencies involved are now aiming to strengthen their relationship with a partnership agreement that will cover not only COVID-19 but also other areas of HTA.

Technology appraisal

In the heat of the pandemic, decisions needed to be made quickly. In transition to a more business-as-usual approach, NICE has undertaken an exploratory scoping exercise for a potential multiple technology appraisal that includes several COVID-19 therapies. Timelines for such an appraisal are still to be determined. Issues that need to be considered include maintaining and updating recommendations as evidence is rapidly generated; linking to clinical work already undertaken within the NICE guidelines; managed access routes; and collaboration between NICE and the commercial activities in NHS England.

Next generation HTA

The HTx Project is an EU Horizon 2020 funded project that is developing methods to improve HTA capability to assess complex technologies. By using a collaborative policy sandbox approach, the HTx Project identified key challenges and developed best practice guidance for HTA of COVID-19 tests and treatments [1], which include recommendations on RWE and a 'living' approach to HTA.

Role of real-world evidence

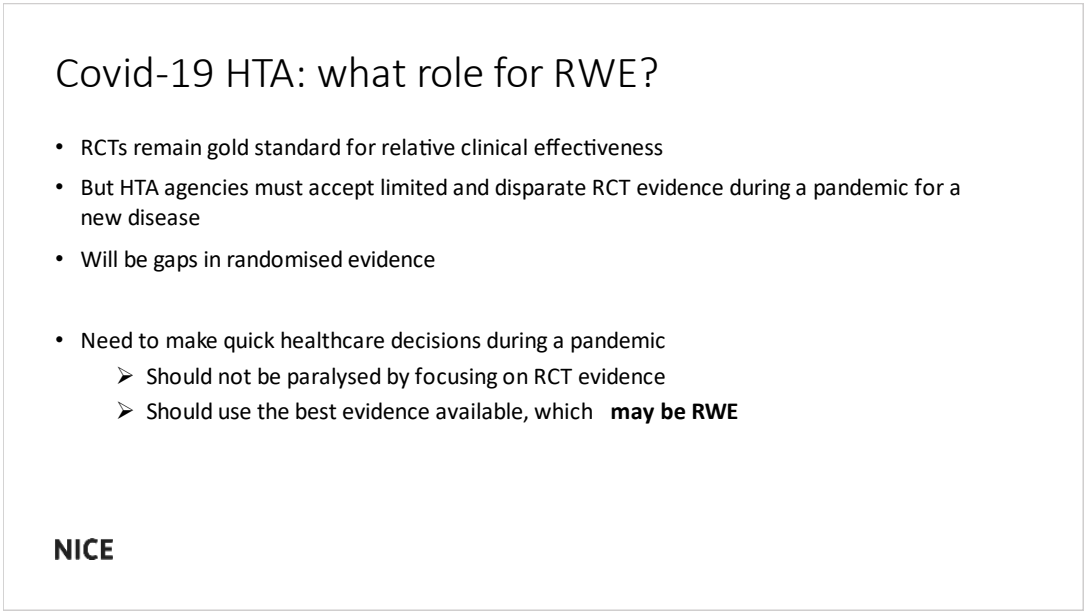
The guidance on RWE described some of the cases where RWE may be suitable (or even superior) to fill certain data gaps. For example, RWE could be used in epidemiology for calculation of the 'R' rate, studying long-term effects of COVID-19 and identifying subgroups of patients with different risk profiles. The recommendations emphasised the need to consider robustness, uncertainty and generalisability, and to utilise available checklists to assess the quality of RWE studies. In addition, federated networks of trusted data sources should be explored and analytical power increased by using novel approaches to combine randomised controlled trial (RCT) and non-RCT evidence.

Living HTA approach

One of the key recommendations in the best-practice guidance was that HTA agencies should explore a 'living' or life cycle approach to COVID-19 assessments. As many COVID-19 therapeutics will soon require HTA assessment, there is a need for HTA agencies to transparently accept that decisions are needed despite uncertainty; rapidly update assessments in response to new evidence; and be willing to update (and reverse) decisions if supported by new evidence. RWE can inform initial assessments while RCTs are few and inform rapid updates as more RWE emerges.

Summary

During the pandemic, NICE played a key role in co-ordinating the RAPID-C19 programme, producing COVID-19 guidelines, developing early economic models and facilitating international collaboration. Going forward, HTA agencies should explore a life cycle approach to COVID-19 assessments and must accept limited and disparate RCT evidence during a pandemic of a new disease. RWE may be the best evidence available and should be used to inform initial assessments, while emergent RWE can inform rapid updates.



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Session 2: RWE for decision making – what are today's opportunities?

RWE for decision making: what are opportunities for today and in the future?

Regulatory viewpoint

Dr John Concato, *Associate Director for Real-World Evidence Analytics, Office of Medical Policy, Centre for Drug Evaluation and Research (CDER), US Food and Drug Administration (FDA)*

The aim of the FDA RWE Programme is to evaluate the use of RWE to support either a new indication for an approved drug or biologic, or to satisfy post-approval study requirements. Its main focus is the implementation of RWE through internal processes, external stakeholder engagement, demonstration projects and guidance development.

RWE demonstration projects

An example of a demonstration project that seeks to improve the quality of RWD is the OneSource project; this aims to ensure that the right clinical data is entered only once and then used many times. The project involves standards-based tools within the electronic health record (EHR) to bring together healthcare and research e.g. populating electronic case report forms directly from EHRs.

More recent RWE demonstration projects supported by FDA are focusing on enhancing evidence generation by linking randomised controlled trials (RCTs) to RWD; applying novel statistical methods to develop a decision framework for hybrid RCT designs, combining internal control arms with data from RWD sources; transforming RWE with unstructured and structured data to advance tailored therapy; and advancing standards and methodologies to generate RWE from RWD through a neonatal pilot project.

RWE guidance

FDA issued a draft RWE framework in 2018, and towards the end of 2021, published four RWE draft guidance documents to inform stakeholders about FDA's current thinking on topics related to RWD and regulatory considerations:

1. **EHRs and medical claims data** – includes recommendations on how to select relevant data sources, as well as how to define and validate study variables [1].
2. **Registries –** provides recommendations on designing or using an existing registry to support regulatory decision making [2].
3. **Data standards –** advises sponsors to document the rationale for any changes made in submissions with RWD, to ensure that RWD conforms to current FDA data standards [3].
4. **Regulatory considerations** – describes FDA's expectations regarding non-interventional or observational studies that only use RWD [4].

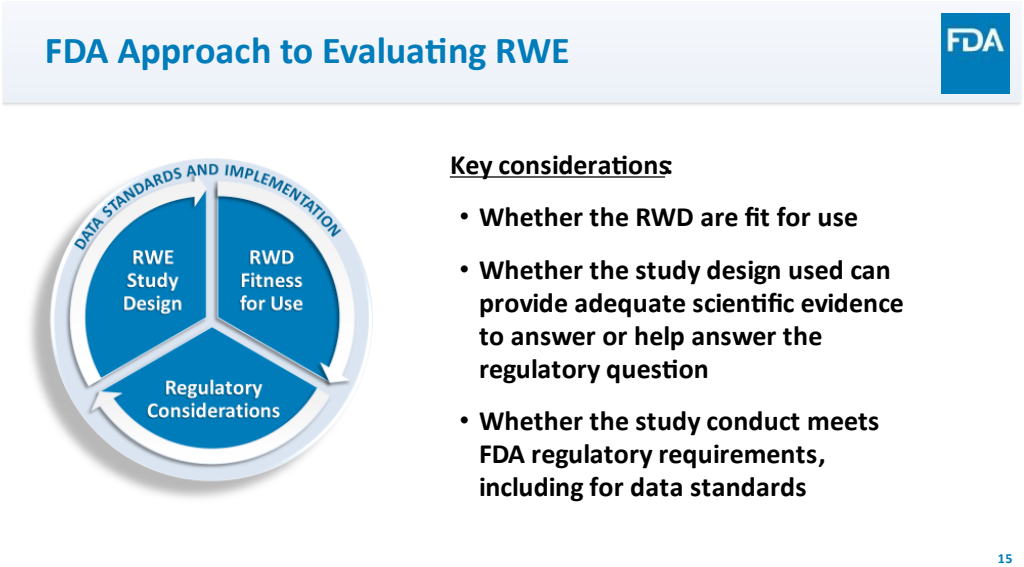
Additional RWE guidance is being developed in 2022, including considerations for the design and conduct of externally controlled trials and using clinical practice data in RCTs.

FDA approach to evaluating RWE

FDA promotes consistency in its evaluation of RWE for effectiveness in various ways (see below). A key approach is to assess whether the data are fit for use for the clinical context, whether the study design provides adequate scientific evidence to answer the regulatory question and finally, whether the study conduct needs regulatory requirements, including for data standards.

The example of tacrolimus demonstrates how RWE was used by FDA to approve a new indication. Tacrolimus was approved for prophylaxis of organ rejection in patients receiving liver transplants in 1994 based on RCT evidence. It has since been used widely in clinical care, including for lung transplant, and more recently, the sponsor submitted a supplemental new drug application to FDA. Following evaluation of the study data and design as well as application of FDA standards, an approval for preventing rejection or death after lung transplant was granted in July 2021.

The data came from the US scientific registry of transplant recipients and the study design was a non-interventional (observational) treatment arm, compared to historical controls. A review by FDA determined that this study was, "adequate and well-controlled," which is a necessary requirement for drug approval at FDA. It was also noted that the outcomes of organ rejection and death are virtually certain without therapy, and so the dramatic effect of treatment helped to preclude bias.



RWD/E and COVID-19

RWD continues to accumulate as the pandemic unfolds, however, more RWD is not always better. Challenges in diagnosing, treating, and reporting on a new disease can create methodological problems. Scientific rigor must be maintained to be able to leverage RWD to inform clinical and regulatory decisions on COVID-19.

Summary

FDA's RWE Programme has delivered on the plan described in the agency's 2018 framework document and continues to evaluate RWD/RWE. Looking forward, it is important to recognise that all data sources and study designs have strengths and limitations, and analyses involving RWD and RWE have distinctive attributes. Other study designs can supplement—but not replace—traditional clinical trials for regulatory decision making. Clear and consistent use of terminology can advance understanding and ongoing collaborative efforts can help to identify factors that promote generation of robust RWE.

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RWE for decision making: what are opportunities for today and in the future?

Payer viewpoint

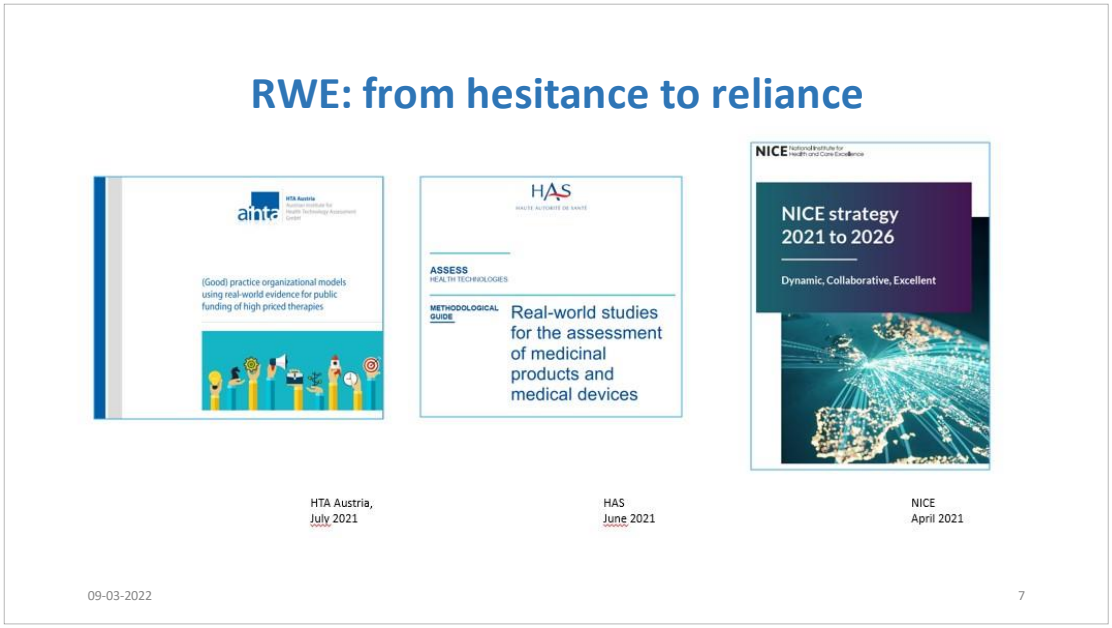
Jo de Cock, *Former CEO, National Institute for Health and Disability Insurance, Belgium*

Although RWE is not a new science, payers are becoming increasingly interested in RWE. This is being driven by the need to reduce uncertainties at market launch; opportunities offered by digital developments; and policy developments, such as the EU Pharmaceutical Strategy and EU Health Data Space. Nevertheless, payers remain cautious about the use of RWE and have different concerns to other stakeholders.

Barriers to using RWE

A study of payers in the US showed that a variety of barriers are perceived to implementing RWE in outcome-based contracts, the most significant being the definition of outcomes and complexity of agreements [1]. For European HTA agencies, the two most important barriers to accepting RWD were lacking necessary RWD sources and existing policy structures [2].

Many payers and HTA agencies are considering how to remove these barriers and have produced guidance on RWE, demonstrating a move from hesitancy to reliance on RWE (see below). However, further development is still required to work towards a consensus-driven research agenda, an appropriate RWD/E infrastructure, standardised processes for validating RWD, adopting best practices for critical appraisal of RWE and expanding use cases of RWD/RWE in decision making [3].



RWE4Decisions: a collaborative initiative

RWE4Decisions was commissioned by the Belgian National Institute of Health and Disability Insurance to explore the potential use of RWD in payer/HTA decisions with all stakeholders, including policy makers, HTA bodies, payers, regulatory agencies, clinicians, patient groups, researchers, industry and academic experts. The RWE4Decisions initiative was set up as a learning network based on two key principles: collaboration, which means shared responsibility of different stakeholders and iterative dialogues throughout the technology life cycle, and transparency, including publishing methods and sharing information. The role of each stakeholder group in RWE4Decisions has been identified, as well as

recommended actions for each group to support the generation, analysis, and interpretation of RWD to inform decision making [4].

In 2021, RWE4Decisions held workshops for its stakeholders that had a key focus on RWE and outcomes-based managed entry agreements. These led to a set of potential actions that could be taken by individual stakeholders or collaborative initiatives [5]:

1. National or collaborative horizon scanning processes are needed to identify eligible technologies for outcomes-based managed entry agreements.
2. HTA/payers need to clarify the decision relevant uncertainties and identify key clinical questions and the data to be collected.
3. Outcomes-based managed entry agreements should only be initiated when sufficient data can be collected to resolve decision relevant uncertainties.
4. For rare diseases, collaboration across countries is needed to align data requirements and access to datasets.
5. Processes need to be developed to interact with regulators to avoid duplication and to use the Data Analysis and Real-World Interrogation Network (DARWIN EU)
6. A proactive approach to data collection must involve all relevant stakeholders.
7. Data collection plans should be clearly documented and publicly reported.
8. Financial investment in data infrastructure, collection and analysis is necessary.
9. RWE4Decisions should support development of relevant guidance relating to generation of RWE in HTA/payer decision making.
10. Connection with collaborative initiatives such as Beneluxa or FINOSE could lead to additional outcomes.

Summary

RWE is not a ‘magic bullet’ or a standalone issue; it can be a vital part of integrated evidence generation plans. Ongoing structured and iterative dialogue among stakeholders along the product life cycle should be developed further. There is a need to move away from fragmented recommendations to comprehensive guidance and improvement of standards of RWD studies. Outcomes-based managed entry agreements should contain a clear RWE generation plan. Practical learnings must be shared to support decision makers; this could be facilitated through a learning network.

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Utility of RWD in regulatory decision making

RWE for decision making: what are opportunities for today and in the future?

Company viewpoint

Prof Thomas Kuhler, *Head of Global Regulatory Science and Policy for EU/AMEE, Sanofi*

To explore the utility of RWD in regulatory decision making, Sanofi commissioned two studies using the Cortellis database. The first study focused on new drug applications and line extensions submitted to the European Medicines Agency (EMA), US Food and Drug Administration (FDA), Health Canada and Japanese Pharmaceuticals and Medical Devices Agency (PMDA), while the second focused on the post-marketing surveillance activities of products that had a marketing authorisation approved by the EMA and the FDA.

New approvals and line extensions

The first study showed that there were 17 new drug applications submitted between 1998-2018 and 10 line extensions between 2012-2019 in which regulatory approval was associated with RWD [1]. The main drivers of RWE acceptability were often rare diseases, significant unmet need, or where randomised controlled trials were unfeasible.

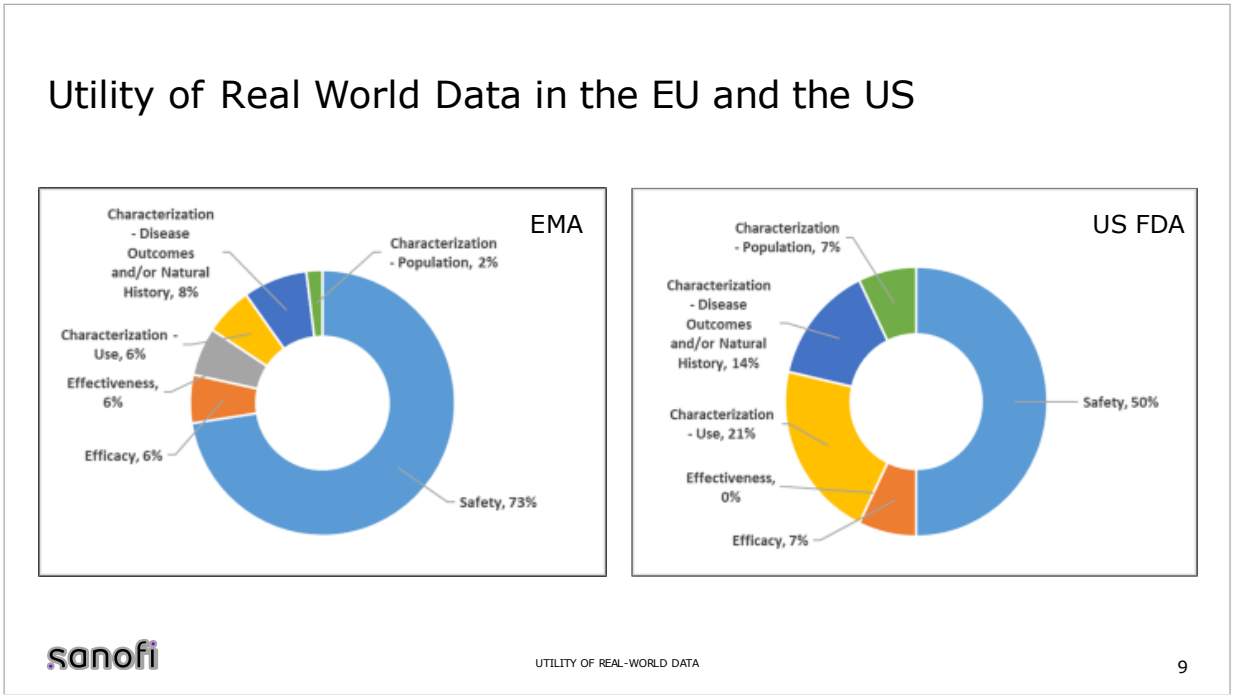
The majority of new approvals associated with RWD were for children and adults (61%) whereas the majority of line extensions were for adults only (50%). With regards to therapeutic area, most products for which RWD were applied in new drug applications were for use in oncology and metabolism, while for line extensions, RWD applications were spread across therapeutic areas. The source of the RWD for both new approvals and line extensions was mainly medical records and registries.

Post-marketing activities

The second study found data covering the last 14 years for the EMA and data spanning back 23 years for the FDA [2]. A total of 165 cases in which RWD was used in the post-approval setting were identified: 109 were approved by the EMA between 2007 and 2020 and 56 approved by the FDA between 1998 and 2020. An increasing number of products were approved in recent years, with the highest number of approved products in 2018 (30 products) for the EMA and in 2019 (19 products) for the FDA. However, from 2019 to 2020, there was a notable drop in approvals, which could be an effect of the COVID-19 pandemic altering the focus of the entire pharma sector.

Most products approved with post-marketing surveillance were small molecules (61% for EMA, 62% for FDA) and a wide range of therapeutic areas were represented. Registries were the most common RWD source for both EMA and FDA, however, there was variation in the type of registry used by each agency; patient registries and product registries were almost evenly used by EMA (49% vs 48%, respectively), whereas the FDA mainly used product registries (85%).

Data from post-marketing surveillance activities were also classified based on the objective or utility of the RWD (see next page). This showed that RWD was mainly collected to verify the safety profile of the drug (73% for EMA, 50% for FDA).



Summary

Utility of RWD/RWE should not be underestimated, as in recent years it has been increasingly used for new product approvals, line extensions and in the post-approval setting. For new approvals and line extensions, utility of RWD is primarily to meet unmet medical needs and/or where randomised controlled trials are deemed unfeasible, while in the post-approval setting, RWD is more likely to be used to verify safety.

There is growing appreciation that RWD is a source in its own right to support regulatory decision making. Sanofi research demonstrates that RWD is a flexible and innovative means to generate actionable evidence that has become accepted by major regulatory authorities.

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RWD and RWE: Brazilian perspectives

Regulatory acceptance and use of RWD generated within and from other jurisdictions – what are the challenges and how are agencies adapting?

Regulatory viewpoint

Gustavo Mendes Lima Santos, *General Office of Medicines and Biological Products (GGMED), Brazilian Health Regulatory Agency (ANVISA)*

There is currently no specific guideline on the submission of RWD in Brazil; many concepts of RWD are still under discussion. Nevertheless, RWD is already submitted to ANVISA for the purpose of generating safety evidence, such as from observational or pharmacoepidemiological studies. In some cases, RWD is also submitted to generate efficacy evidence, such as from single arm studies with a historical response rate based on data review, patient records, expanded access or other clinical practices. These cases are often in rare diseases or oncology.

Uses and sources of RWD

There are several potential uses of RWD in Brazil, including generating hypotheses to be tested in control and randomised studies, identification of clinical drug development tools and measuring the ability to carry out a study by examining the impact of inclusion/exclusion criteria on the population. In addition, RWD can be used in generating information about probabilities in Bayesian statistical models, identifying prognostic indicators or baseline characteristics of patients for stratification and gathering data from cohorts in different locations. All of these potential uses listed in ANVISA's considerations are based on international discussions that the agency is having with other regulatory agencies, which are helping ANVISA to better understand where it can use this sort of data.

Potential sources of RWD in Brazil are either from public data, such as the DATASUS data bank, or private data. Private data may come from observational studies, patient registries and pharmacovigilance activities.

Using RWD for regulatory decisions

Key questions for regulators to consider when using RWD for decision making are:

- Is the RWD suitable for regulatory use?
- Can the study design provide adequate scientific evidence to help answer regulatory questions?
- Does the study meet regulatory requirements (data collection, monitoring, Good Clinical Practices)?

Assessing the adequacy of RWD is essential. Regulators must consider data quality, standardisation, collection and validation to be confident that the RWD is traceable and consistent.

Registries can have limitations in regulatory decision making. In Brazil, there is still a lack of standardisation of terms in historical registry data and access to registry records can be difficult. In addition, different formats are often used to report information and there can be issues integrating data from different sources for a single patient.

With regard to observational studies and pharmacovigilance, lack of prior transparency is a potential issue. Due to the low cost of evaluating this data, it can be analysed repeatedly until the wanted results are obtained; it is critical to have procedures in place to prevent such practices.

Summary

Challenges to using RWD in regulatory decisions include issues around data quality and data validation. Use of registries can be limited by lack of standardisation, poor access, inconsistent report formats and difficulty in integrating data from different sources for a single patient. Transparency can be an issue with observational and pharmacovigilance studies; there must be regulatory procedures to prevent excessive analyses to generate the result wanted. In Brazil, there is a need to standardise the terms and rules for RWD use and evaluation; this must involve collective work between regulators, industry, agencies and academia.

Regulatory acceptance and use of RWD generated within and from other jurisdictions – what are the challenges and how are agencies adapting?

Regulatory viewpoint

Junko Sato, *Office Director, Office of International Program, Pharmaceutical and Medical Devices Agency (PMDA), Japan*

RWD comes in several forms, such as electronic health records and health insurance claim data. It is also derived from various sources, for example, databases, registries and published scientific articles. The purpose or utility of RWD may be for new drug applications, post-marketing studies, identification of safety signals or development of guidelines.

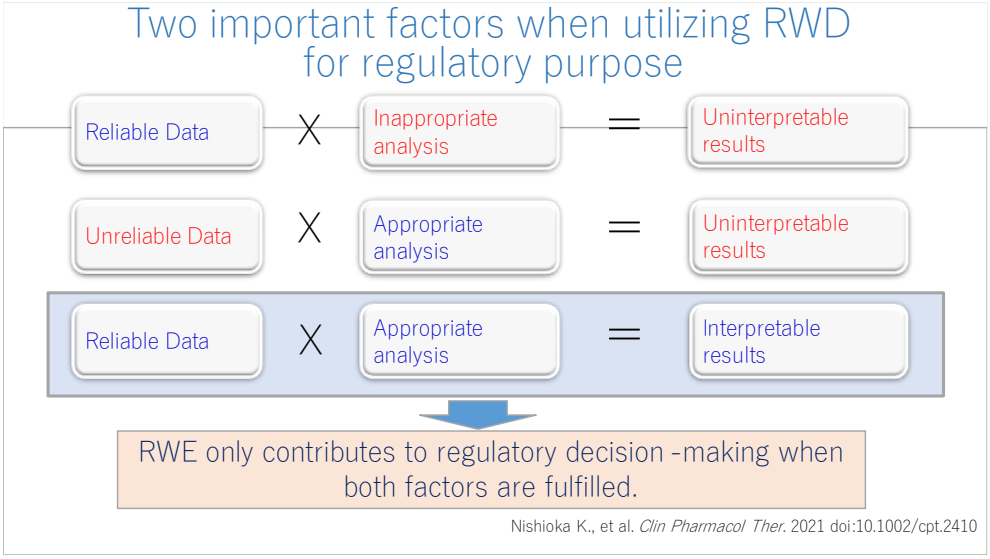
PMDA experience of RWD

PMDA has been using RWD for regulatory approval decisions since 2007. For example, in June 2013, PMDA approved tacrolimus for the treatment of interstitial pneumonia in patients with polymyositis or dermatomyositis based on survival rates from a retrospective cohort study used as a comparator.

The Medical Information Database Network (MID-NET) is an electronic medical records database covering 23 hospitals and over 5.7 million patients in Japan. It was established by PMDA for real-time assessments of drug safety and became fully operational in April 2018. Although the main purpose of MID-NET is for post-marketing drug safety assessment, PMDA revised utilisation guidelines in April 2021 to allow MID-NET to be used in studies required for new drug applications. Examples of utilisation includes analysis of a prescription trend, evaluation of safety in off-label use and evaluation of efficacy.

Issues with utilising RWD

To utilise RWD in for new drug applications, it is critical to pay attention to its characteristics, reliability, quality and limitations. There are two key factors to utilising RWD for regulatory decision making: reliability, in terms of accuracy, consistency and completeness of the RWD; and appropriateness of the analytical method used in the study (see below). If one of these factors is missing, the result will be uninterpretable.



PMDA's efforts toward utilisation of RWD

In April 2021, PMDA established a new working group for RWD, which will drive implementation of the guidelines on patient registries; share experience and knowledge on patient registries; and discuss all RWD subjects comprehensively, including general principles on RWD utilisation and data reliability in the regulatory setting. Through the activity of the working group, PMDA plans to strengthen RWD utilisation throughout the product life cycle, from pre-approval to the post-marketing phase, towards enhancement for early patient access.

In order to facilitate RWD utilisation, PMDA established new scientific categories for product development using registry data. PMDA has also developed two guidelines that were issued as notifications by the Japanese Ministry of Health, Labour and Welfare.

Basic Principles on Utilisation of Registry for Applications

This guideline was developed on the utilisation of registry data for cases such as external control of clinical studies for efficacy evaluation. It provides points to consider on registry patient population, endpoints, evaluation period, statistical method, type of observational study for natural history etc, when using registry data as an external control.

Points to consider for ensuring the reliability in utilisation of registry data for applications

This guideline specifies points to consider for ensuring reliability of registry data, including governance by registry holders and compliance matters for applicants. It also encourages applicants to obtain scientific advice from PMDA, as the level of reliability required for registry data may vary depending on the purpose of utilisation.

Summary

RWD is a useful tool for efficient medical product development and generating robust evidence based on clinical data. However, RWE only contributes to regulatory decision making when both reliable RWD and appropriate analyses are used.

PMDA has used RWE in regulatory approval decisions for many years and is evolving its use through consultation on registry utilisation for applications; implementation of new guidelines on product development utilising RWD; and establishing a working group on RWD. Experience sharing and multi-stakeholder collaboration are essential to accelerating the utilisation of RWD.

Session 3: RWE acceptance by regulatory and HTA agencies for early access medicines - how can this be best achieved and what are the key challenges?

Has the pandemic accelerated the acceptance and utility of RWD/RWE in regulatory/HTA decision making?

Dr Harald Enzmann, *Chair, Committee for Medicinal Products for Human Use (CHMP), European Medicines Agency (EMA)*

The COVID-19 pandemic has demonstrated that RWD can be used successfully and that it is feasible to conduct large, fast randomised clinical trials (RCTs). However, when considering the learnings to take forward into new regulatory rules, it is important to recognise the particularities of the early COVID-19 pandemic; there were a high number of patients, relatively unambiguous clinical endpoints (compared to say Alzheimer's disease), no alternative treatments, recent natural history data and different stakeholder expectations i.e. more acceptance of higher uncertainty.

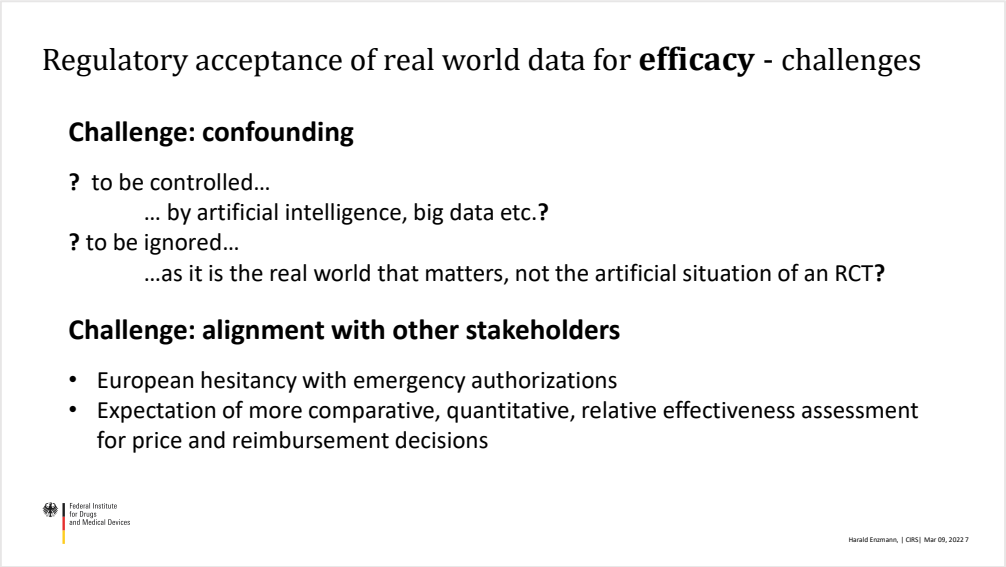
Regulatory acceptance of RWD for safety

An example from the pandemic where RWD flagged a risk was the rare but severe adverse event of vaccine-induced cerebral venous sinus thrombosis. Although the benefit-risk balance for the vaccine remained positive, the detection of this risk was important for informing utility and treatment decisions. It became clear that RWD can have a very high sensitivity for the detection of adverse events. While this may be reassuring for similar situations, the same may not apply to rare diseases or populations with many comorbidities, where safety signals will be noisier and more difficult to detect.

Challenges in accepting RWD for efficacy

There are two key challenges to using RWD for the demonstration of efficacy (see next page). The first is confounding factors, which is an issue that cannot be ignored by the regulators. Although efforts are being made to use artificial intelligence and big data to control confounding, more work is needed to gain regulatory acceptance.

Secondly, stakeholder alignment is a key challenge. For example, during the pandemic, there was hesitancy at the public and political level in most EU member states towards emergency authorisation. In addition, as regulators move towards even earlier approvals and higher acceptance of uncertainties, it is important to avoid a widening gap between regulators, HTA bodies and payers, as this will not be beneficial for patients. Industry cannot expect that the same data for early regulatory approval will be sufficient for price and reimbursement decisions.



Changing mindsets

Regulatory mindsets can often be risk averse, conservative and intolerant to ambiguity. Although RWD has clearly demonstrated its value during the pandemic, the standard RCT has also been shown to be feasible. For this reason, there may still be reluctance from regulators to accept RWD. Instead of pushing for an explicit guideline on the use of RWD right now, the best way forward may be for industry to prepare comprehensive case studies of RWD that are not linked to the pandemic and to present these to the regulators for discussion and as potential basis for regulatory decisions.

Summary

The COVID-19 pandemic has demonstrated the utility of RWD for regulatory decision making and the feasibility of large, fast RCTs. While RWD is widely accepted for safety, there are challenges in its use for efficacy, such as confounding factors and alignment with other stakeholders. Pushing for a guideline on the use of RWD now may be premature and may cement a conservative view among regulators. Therefore, going forward, it may be better to probe the regulatory system with well-prepared cases of RWD that may facilitate acceptance (though not preference over RCTs).

Aligning regulatory and HTA RWE needs, pre- and post-approval, to avoid duplication – what are the challenges and how could this be best achieved?

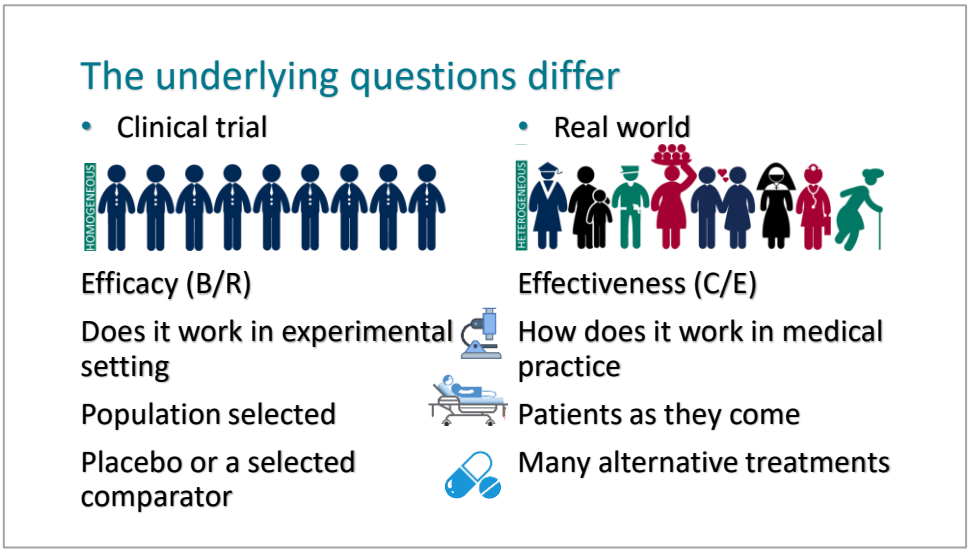
Dr Anja Schiel, *Lead Methodologist/Statistician/Team leader for international HTA, Norwegian Medicines Agency*

Different frameworks, different questions

Regulators and HTA agencies have very distinct decision-making frameworks. The aim of the regulator is to determine whether a benefit has been established and whether this benefit outweighs the risks seen. This benefit-risk decision is based on the current available evidence for a specific product, with some room to accept uncertainties or to decide which uncertainties need to be addressed by additional evidence generation.

In contrast, reimbursement decisions are far less static. They are country-specific, taking into account the respective healthcare systems, and are driven by political, ethical and socio-economic criteria, as well as budget restraints. HTA agencies are tasked with weighting product-specific uncertainty across the entire healthcare system, often using health economic models that predict the future based on available data from different sources. The challenges of using models can be summed up in the famous words of statistician George E. P. Box: *All models are wrong, but some are useful.*

These fundamental differences between regulatory and HTA frameworks mean that the questions each stakeholder needs to answer with data/evidence will also be different (see below). While regulators want to reduce variability to isolate the effect of the intervention and allow a conclusion on causality, HTA agencies embrace variability as it reflects the unpredictable behaviour of patients and their healthcare system.



What, when and how RWD should be generated

Currently there is too much focus on post-launch evidence generation, managed entry agreements and alternative financing schemes; these approaches do not address or remove all uncertainties but instead spread them out over time. Managed entry agreements based on innovative use of RWD would only work if it is possible to reduce uncertainty after the decision has been made, which would rely on the whole decision-making process being adaptive. This is not the case for current decision-making frameworks, which are static in nature.

Evidence gaps can be foreseen and planned for; communication is key to avoiding a potentially unsolvable evidence gap. Decisions on what, when, and how RWD should be collected need to be taken early enough, in parallel with the clinical development programme. These decisions must also be made collaboratively, taking all stakeholder perspectives and frameworks into account.

The 'why' is also important

Although there are huge amounts of data available, more data is usually not the solution to an evidence gap. It is essential that the 'right' data is collected in the right context. The usability of data for all stakeholders would be collectively increased if data were actively collected with the purpose of reducing uncertainty. The identification of where the certainties are and which are to be expected, needs to start early within an iterative and collaborative process.

Not all questions can be answered with RWD; there are areas where the only proper evidence is a randomised clinical trial. The determination of when and for whom RWD is the better tool depends on the nature of the uncertainties that the RWD needs to address, which is something that needs to be negotiated between stakeholders. There must always be a clear understanding of for whom the data was generated for.

Summary

The decision frameworks and underlying questions of regulators and HTA agencies are fundamentally different. Decisions on when, what and how to collect data need to be taken early enough, collaboratively and should respect and reflect the needs of different decision frameworks; effective communication is key to ensuring this. The overall aim of data collection should be to reduce uncertainty in decision making; it is important to understand the decision(s) that follow and which uncertainties need to be removed/reduced.

Strengthening the use of RWE for drugs in Canada

Would an international roadmap for use of RWE in decision making be of value?

Dr Melissa Kampman, *Manager and Senior Epidemiologist, Marketed Health Products Directorate, Health Canada*

R2D2: Improving the regulatory review of drugs and devices

In 2017, Health Canada launched an initiative called 'Improving the Regulatory Review of Drugs and Devices (R2D2)', which aimed to provide more timely access to medicines for Canadians. This initiative included a project, 'Strengthening the use of RWE for drugs', to improve the agency's ability to assess and monitor the safety, efficacy and effectiveness of drugs across the life cycle by optimising the use of RWE in collaboration with stakeholders. Expected outcomes include the increased use of RWE to enhance regulatory decision making, improved sharing of RWE with health system partners, increased clarity for stakeholders who may be interested in leveraging RWE and improved access to drugs through new sources of evidence.

Progress has been made on this project across several areas. For example, consultations were very important in the early phases and Health Canada consulted with the Canadian Agency for Drugs and Technologies in Health (CADTH), Canadian Institute for Health Information and Canada's Drug Safety and Effectiveness Network to identify existing data assets. Health Canada has also posted a notice to stakeholders on its website about RWE, along with an accompanying guidance document on elements of RWD/E quality.

RWD challenges and opportunities

Limitations around the utility of data can be a challenge for regulators. RWD may not be fit for purpose or of high quality, and assumptions around causal interference are not always met. There can also be methodological challenges in transforming RWD to RWE. It is important that regulators have some level of access to the data and can understand its structure, format, endpoints, timing etc.

A considerable amount of RWD already exists, which is greatly beneficial. Large databases with broad ranges of patients can be accessed in a timely manner and quality continues to improve over time. However, there is a need and an opportunity to continue to identify characteristics of RWD that concern regulators; it may then be possible to see how regulators can either harmonise or converge on RWD recommendations internationally.

Use of RWE by Health Canada

In the pre-market space, Health Canada leverages its RWD/E notice and guidance in its reviews and advises sponsors at pre-submission meetings on their use of RWE. The agency has also provided training for its clinical reviewers and developed RWE inventories and standard operating procedures to capture pivotal and novel uses of RWE, which will help to inform future guidance and training.

Post-market RWE is often used in Health Canada's signal detection activities to inform pharmacovigilance and risk management. Health Canada leverages a variety of sources of RWD/E for these activities, for example, environmental scanning, Canada Vigilance data and information submitted from market authorisation holders. New sources continue to be explored internally and with partners.

Importance of collaborations

Health Canada collaborates with a variety of domestic partners to improve the use of RWE. This includes patient group consultations, HTA partners, payers, professional associations and academia. International collaborations remain of key importance, such as the European Medicines Agency Pharmacovigilance Risk Assessment Committee, International Coalition of Medicines Regulatory Authorities RWE and Observational Studies Working Group and international cluster meetings.

Advancing towards a roadmap

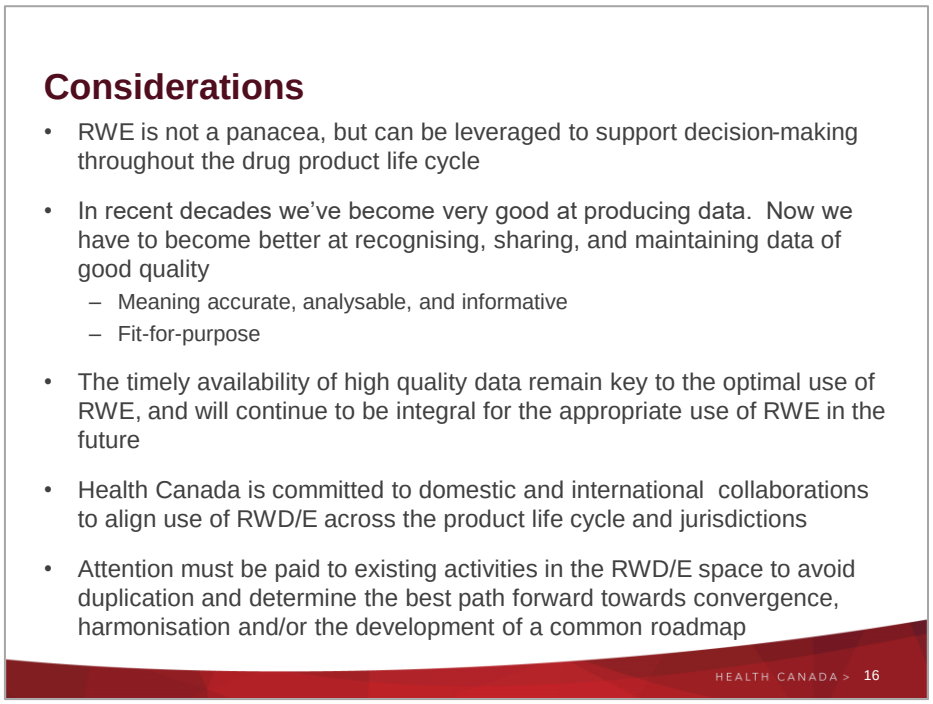
The COVID-19 pandemic has demonstrated how regulators could come together quickly and effectively to leverage RWE across jurisdictions and collaborate on common topic areas/projects. Ongoing collaboration and reviews of data practices during the pandemic will help to optimise the use of RWE within and across jurisdictions.

To advance towards a roadmap for use of RWE in decision making, there must be a multi-stakeholder approach; refinement through a collective body of work that avoids duplication; incorporation of learned lessons; leveraging of a variety of data from different sources, including directly from data holders; and better leveraging of prospective studies and drug/disease registries. It is also important that stakeholders recognise the inherent disorder of RWD/RWE and keep an open mind on its use.

Summary

RWE can be leveraged to support decision making throughout the drug product life cycle. Improvements have been made in producing data but now there must be better recognition, sharing and maintenance of high-quality data; timely availability of high-quality data remains key.

Health Canada is committed to domestic and international collaborations to align the use of RWD/E across the product life cycle and jurisdictions. Attention must be paid to existing activities in the RWD/E space to avoid duplication and determine the best path forward towards convergence, harmonisation and/or the development of a common roadmap.



Would an international roadmap for use of RWE in decision making be of value?

Company perspective

Bart Barefoot, *Director, RWE Policy & Advocacy, GlaxoSmithKline*

In response to the question posed by CIRS, an international roadmap on the use of RWE in decision making would indeed be of value. A proliferation of RWD/RWE frameworks, guidelines and recommendations will make the RWE environment increasingly difficult to navigate for both research sponsors and decision makers, in terms of what should be expected and what is good practice in a particular situation. International alignment and harmonisation will help to drive efficiencies in product development and evaluation, improve consistency in study quality and evaluation, and ultimately support timely delivery of innovative medicines.

What is the desired roadmap destination?

It may be unrealistic to expect a singular global roadmap across both regulatory and HTA contexts, as regulators and HTA bodies have different missions, different questions and different maturities of mechanisms for international collaboration. There might be two different but closely linked roadmaps. In the regulatory context, the ultimate destination should be an International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guideline on principles for using RWD to assess not only product safety but also efficacy and effectiveness. In the HTA context, given the challenges for harmonisation, a viable destination would be to seek to align guidelines to the extent possible.

In neither case should RWE guidelines be prescriptive; flexibility is required given the diversity of data types, data sources and study designs. All stakeholders will benefit from pre-specification of points to consider for evidence planning and evaluation, and sponsors will always need to engage with regulators and other decision makers to discuss the specifics of a proposed RWE study.

Roadmap principles

Building on experience and knowledge gained

Lessons learned from the COVID-19 pandemic must be leveraged when developing the RWE roadmap. It is also critical to build on the experience of longstanding uses of RWE, such as in pharmacovigilance, pregnancy registries and rare diseases.

Build with modular blocks

The use of a modular block approach corresponding to the research process will help to build toward comprehensive aligned/harmonised guidelines [1]. For example, there may be blocks on engagement processes, data sources, study design, analytic methods, study reporting, data submission and final report evaluation. Relevant existing guidelines, recommendations and gaps would be identified in each of the modular blocks, and then gaps addressed through use cases and pilot projects. The final step would be to seek alignment/harmonisation within each block. An example that would fall under the study design block is ongoing work by the ISPE/ISPOR Joint Task Force to harmonise protocol development templates and recommendations for hypothesis-evaluating studies making secondary use of RWD.

Build together iteratively

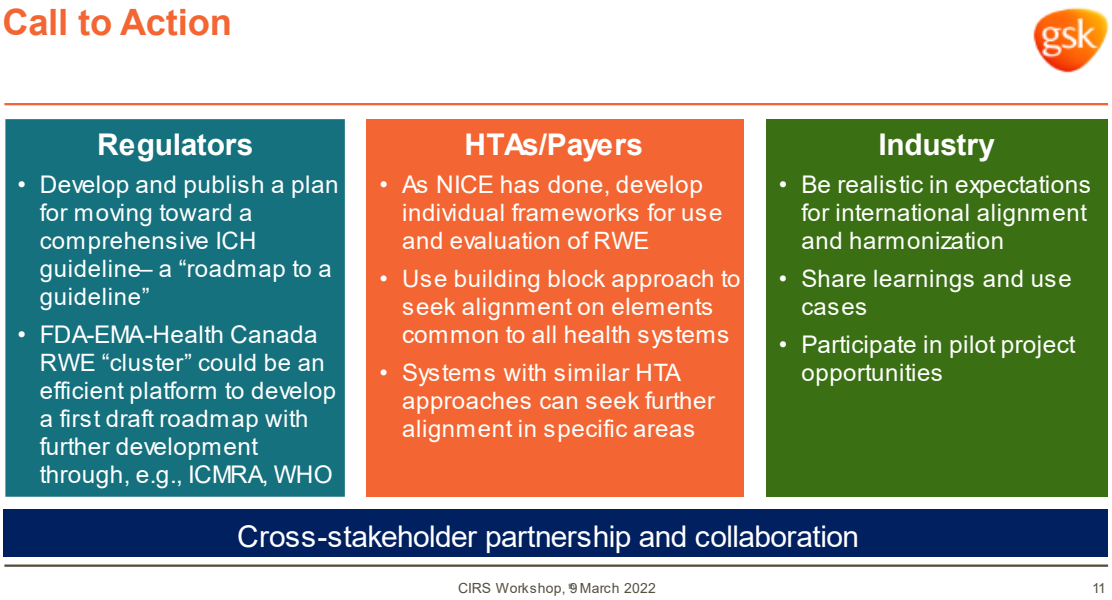
RWE guideline development and alignment should not occur in a vacuum; partnership and collaboration are essential. Multi-stakeholder platforms, such as CIRS, the Duke-Margolis RWE Collaborative and GetReal Institute, should be leveraged for experience sharing, learning and working toward alignment. There needs to be an iterative 'test and learn' approach, using demonstration/pilot projects where needed to address uncertainties.

Call to action for stakeholders

To move forward in the RWE area, each stakeholder must partner and collaborate as well as play their own individual role (as shown below). The regulatory community should develop and publish a plan for moving toward a comprehensive ICH guideline. Development of this plan could start with the FDA-EMA-Health Canada RWE cluster, and then be further developed through broader international regulatory fora, such as the International Coalition of Medicines Regulatory Authorities (ICMRA).*

HTA bodies and payers should continue to develop their own RWE frameworks, using a building block approach to reach alignment in areas where there are commonalities across healthcare systems. It may then be possible for systems that use similar HTA approaches to supplement this with further aligned guidelines that reflect the shared nuances in their approaches.

Finally, industry needs to be realistic in its expectations for alignment and harmonisation, both in terms of what this looks like and the speed with which it can be achieved. Industry must also play its part in the iterative learning process by being willing to discuss experiences and participate in pilot project opportunities.



* Post-meeting note: Following an ICMRA workshop in June 2022, which was co-chaired by FDA, EMA and Health Canada, ICMRA has published a statement that sets out an ambition for regulators to collaborate in four RWD/RWE focus areas through existing fora, including ICH. See https://www.icmra.info/drupal/sites/default/files/2022-07/icmra_statement_on_rwe.pdf

Summary

International roadmap(s) for use of RWE in decision making would be of value to all stakeholders. However, different decision-making contexts may require distinct but linked roadmap destinations. For example, in the regulatory area, the ultimate destination could be ICH guideline(s) encompassing efficacy/effectiveness uses, while in the HTA/reimbursement context, the target may be internationally aligned guideline(s) to the extent possible.

To make progress towards an international RWE roadmap, three development principles must be followed: build on experience and knowledge already gained, build with modular blocks and build together iteratively. These principles should be underpinned by cross-stakeholder partnerships and collaboration.

References

[1] Jaksa A, Wu J, Jónsson P, Eichler HG, Vititoe S, Gatto NM. Organized structure of real-world evidence best practices: moving from fragmented recommendations to comprehensive guidance. J Comp Eff Res. 2021;10(9):711-731. doi:10.2217/cer-2020-0228

Session 4: Life cycle approaches for regulatory, HTA and payer decision making on early access medicines – what is the role of RWE?

What is the value of routine practice data and how should this be factored into decision making?

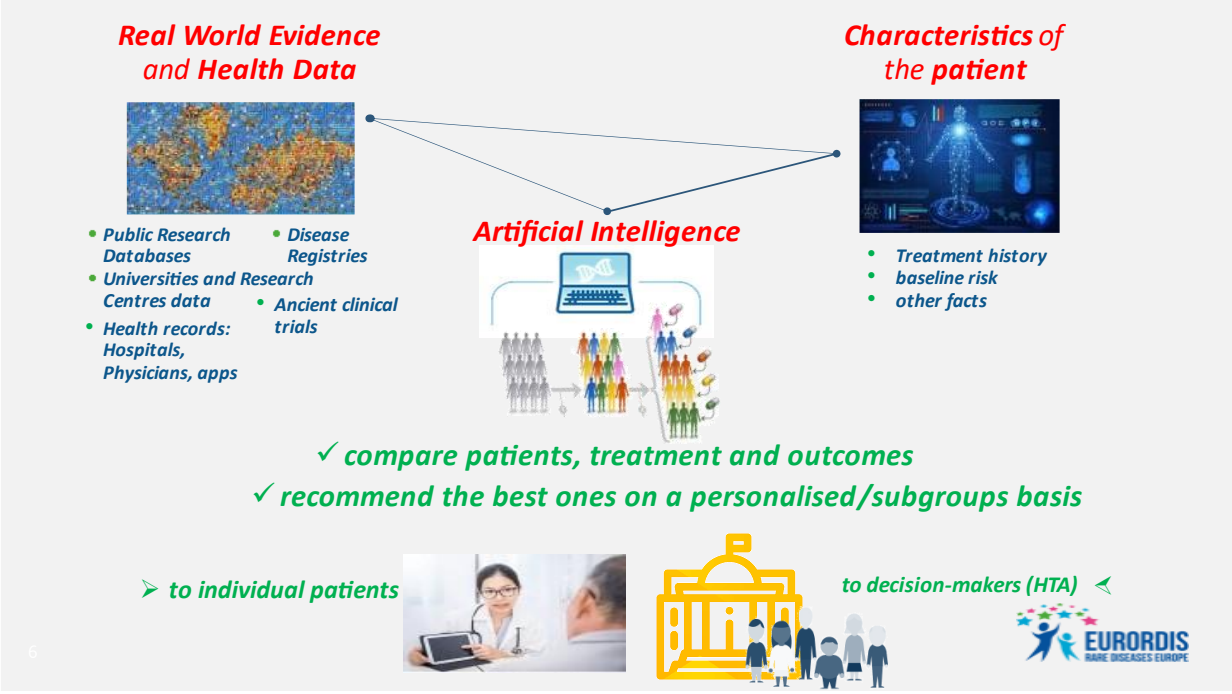
François Houÿez, *Director of Treatment, Information and Access, Eurordis*

The term 'routine practice data' may be more appropriate than RWD because clinical trials are not artificial from the patient's perspective; they are part of real life. Patients want to ensure that the results that come from routine practice data analysis provide answers to the initial research questions.

Routine practice data holds promise

RWD or routine practice data has many promising uses within R&D. For example, routine practice data can help to improve understanding of the natural history of a disease, identify patients matching inclusion criteria for clinical trials, identify controls for case control studies and quantify the prevalence/incidence of diseases. In addition, it can be used to define standard of care, which helps to inform orphan drug designations decisions and comparator choice discussions in scientific advice.

After marketing authorisation, routine practice data can be used at the population level to confirm benefit, confirm safety, measure duration of effect, compare outcomes in similar patients using different treatments and compare outcomes and costs. At the individual patient level, routine practice data can be used to make individual predictions (prognosis) and treatment decisions based on these predictions. Work is underway to utilise artificial intelligence algorithms for this purpose (see below).



Patients can help to address data gaps

To make full use of routine practice data, healthcare settings need to be transformed. Currently the capacity and capability of hospitals to input data to a high standard is limited. Patients could play a role in addressing this gap by using mobile sensors and digital connected devices that can generate an abundance of data that could enrich the content of healthcare databases. For example, patients with idiopathic pulmonary fibrosis can use handheld spirometry at home to submit daily digital readings.

The validation of these digital tools is key to supporting regulatory qualification of novel methodologies for medicine development. An example where this has been done successfully is within the Duchenne muscular dystrophy community, where patients worked with academics, industry and regulators to validate a wearable device that can be attached to the foot to measure mobility. This led to the first wearable-derived digital clinical outcome assessment qualified by the European Medicines Agency for use as a secondary endpoint in trials for Duchenne muscular dystrophy [1].

Summary

RWD or routine practice data holds promise for R&D, for example, in identifying patients for trials, and post-authorisation, such as pharmacovigilance in larger populations. However, there are many outstanding questions around the conclusiveness and robustness of RWD compared to trial data; who should pay for RWD; who should have access to RWD; are patients informed when RWD are used; and whether RWD should be a public good. As healthcare systems are not well equipped to input data to a high standard, patients could instead play a role in gathering RWD by using mobile sensors/digital devices.

References

[1] Servais L, Camino E, Clement A, et al. First Regulatory Qualification of a Novel Digital Endpoint in Duchenne Muscular Dystrophy: A Multi-Stakeholder Perspective on the Impact for Patients and for Drug Development in Neuromuscular Diseases. Digit Biomark. 2021;5(2):183-190. Published 2021 Aug 5. doi:10.1159/000517411

Panel discussion:

RWE as a life cycle approach and dynamic assessment of medicines – is this a practical future?

Each panellist was asked to provide their thoughts on the future utilisation of RWE as part of a life cycle approach to development, review and reimbursement. A summary of key points from each panellist's presentation is provided below.

Patient perspective

Valentina Strammiello, *Head of Programmes, European Patients Forum*

- RWE has value for patients in helping to advance research and accelerate access to medicines.
- However, healthcare systems need to adapt to realise this potential and HTA systems need to develop strategies and methods to be able to make decisions on RWE.
- The role of patient organisations in collecting RWE e.g. through registries should be given more recognition and investment to overcome capacity and capability barriers.
- Dynamic assessments can facilitate patient access to innovative treatments but there needs to be clear management and communication if the final assessment is negative.

Company perspective

Adrian Griffin, *Vice President for HTA & Reimbursement Policy, Johnson & Johnson*

- In the past, RWE was commonly used to complement clinical data in regulatory and HTA submissions.
- RWE is now integrated into evidence generation and is an integral component of a product's value across the life cycle.
- The future of RWE lies in real time evaluation and decision making:
  - Both regulatory and HTA agencies are actively developing new pathways and initiatives
  - COVID-19 has advanced real time trend reporting and interactive data visualisation
  - There is an opportunity for consensus with the EU HTA Regulation
  - Increasing data capture via digital tools and advanced analytics will provide new challenges and opportunities for decision making across the life cycle.

Regulatory agency perspective

Claus Bolte, *Head of Sector Marketing Authorisation, Swissmedic*

- RWE is already being used as part of a life cycle approach to medicine assessment:
  - Pre-marketing e.g. epidemiology, rare diseases, patient centred drug development
  - Post-marketing e.g. Periodic Benefit Risk Evaluation Report (PBRER), post-authorisation safety studies, expanded access programmes
  - Operationally e.g. registries, pragmatic trials, claims databases
- There is a need to discuss the use of claims databases, electronic health records and historical controls in the pre-marketing area.
- The Access Consortium is exploring the use of RWD/E in clinical trial design and regulatory approaches as well as use of RWD to support early market entry of COVID-19 vaccines and therapeutics.

HTA agency perspective

Andrew Mitchell, *Strategic Adviser, Evaluation, Australian Government Department of Health*

- There is a practical future to using RWE as part of a life cycle approach, though HTA agencies may use this approach sparingly and with caution.
- To better understand global meaningfulness of locally acquired RWE, transparent multinational collaborations are needed.
- The COVID-19 pandemic provided useful lessons for the life cycle approach but these may not be applicable to the main work ahead in rare populations.

Payer perspective

Dr Daniel Erdmann, *Team Lead, GKV-Spitzenverband, Germany*

- Pharmaceutical companies are responsible to provide the best possible studies (ideally blinded) to inform the basis for first approval.
- Data accessibility is an issue; results need to be accessible to all relevant parties for longer.
- Legal regulations must ensure that data is collected from the first day a drug is used.
- Regulatory and HTA processes need to be strengthened to ensure RWE does not become a substitute for usual requirements.

Summary of panel discussions

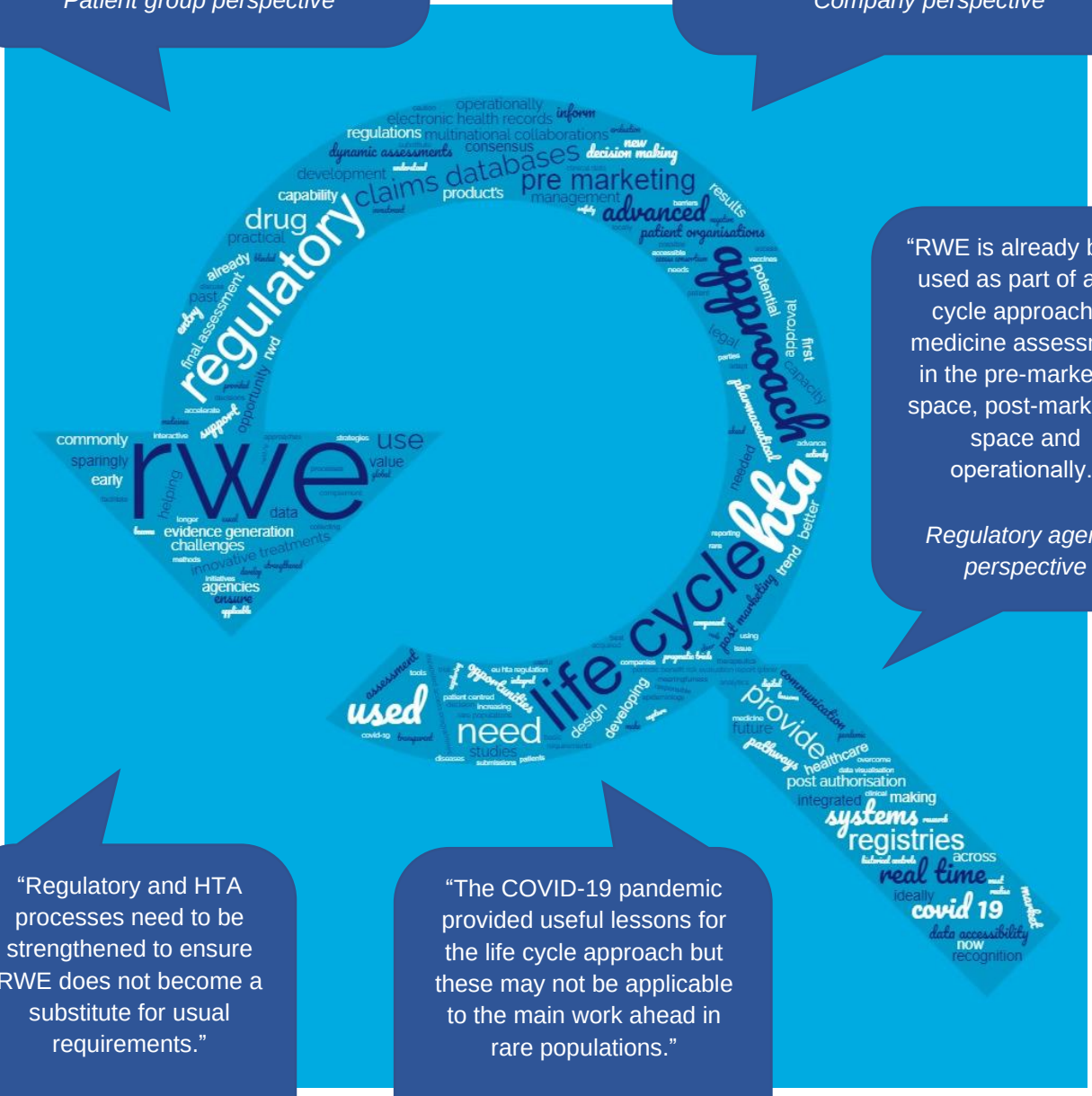
Stakeholder reflections on the future utilisation of RWE as part of a life cycle approach to development, review and reimbursement

"The role of patient organisations in collecting RWE should be given more recognition and investment to overcome capacity and capability barriers."

Patient group perspective

"The future of RWE lies in real time evaluation and decision making, with opportunities in new regulatory and HTA pathways, the EU HTA Regulation and advanced tools/analytics."

Company perspective



"RWE is already being used as part of a life cycle approach to medicine assessment in the pre-marketing space, post-marketing space and operationally."

Regulatory agency perspective

"Regulatory and HTA processes need to be strengthened to ensure RWE does not become a substitute for usual requirements."

Payer perspective

"The COVID-19 pandemic provided useful lessons for the life cycle approach but these may not be applicable to the main work ahead in rare populations."

HTA agency perspective

Section 3: Breakout discussions

Breakout discussion A

How could RWE shape a more predictive process of "efficacy to effectiveness assessment"?	
Chair	**Niklas Hedberg,** *Chief Pharmacist, TLV, Sweden*
Rapporteur	**Sang Mi Lee,** *Access Lead, Personalized Healthcare, CGP and Tumour Agnostic Portfolio, F.Hoffmann-La Roche, Canada*

Background

RWD/RWE can bring value to every stage of a drug's life cycle. Although regulatory and HTA submissions are likely to remain focused on randomised controlled trials (RCTs) in the future, these are also likely to be supplemented with RWD/RWE as agencies and companies increasingly recognise the value of real-world late phase trials. Indeed, the increasing use of RWD and RWE to support clinical development pre- and post-approval has been accelerated by the pandemic.

However, especially for medicines which have gone through an expedited regulatory process, the evidence on relative effectiveness and risks of new health technologies that is available for HTA at the time of a marketing authorisation application, is often limited. Data insufficiencies on treatment effects, safety and costs at the time of HTA assessment are often a concern and having good quality data is important to minimise uncertainty in reimbursement decision making. As new medicines are brought to market utilising expedited regulatory processes and increasingly complex technology, there is an increased need for fit-for-purpose RWD and RWE as an addition to data from traditional RCTs. The question is, can the evolving use of RWE shape a more predictive process in assessing the "efficacy-effectiveness data gap" for decision makers?†

The key consideration for this breakout is to discuss the role that RWE could have to shape a more predictive process of "efficacy to effectiveness assessment" and what needs to be considered for RWE to close the efficacy-effectiveness data gap.

This breakout was therefore asked to build on the workshop discussions, with the following objectives to discuss:

- How could RWD/RWE shape a more predictive development process by more clearly bridging the efficacy to effectiveness assessment gap, thereby setting the stage for having available more robust information for regulatory and HTA decisions?
- What are the main areas and what are the current or perceived challenges for RWE to play this role?
- Providing help for use of RWD/RWE in the closing of the efficacy-effectiveness gap, what needs to be considered to support this so such data can reach its potential – what are the policy/research needs to address the key challenges?

† The "efficacy-effectiveness gap" is the discrepancy between the real-life efficacy of a drug and the outcome of the same drug in a standardised environment under ideal conditions in the context of RCTs.

Discussion results

Q1a. Is there a role for RWD/RWE to shape a more predictive process to address the efficacy-effectiveness gap?

The breakout group agreed that **RWD/RWE is already being used to address the efficacy-effectiveness gap**. For example, in the area of vaccines, there have long been post-marketing commitments for long term effectiveness study. Clinicians are also already using RWD/RWE, which is impacting clinical practice and the wider healthcare system. Therefore, the breakout group felt the key question to answer is, **when does RWD/RWE not have a role** in addressing the efficacy-effectiveness gap? It may be more helpful to **consider RWD/RWE as part of a holistic data package** that is needed to address the efficacy-effectiveness gap, rather than as a solution for closing the gap.

The group also discussed differences between regulators and HTA agencies in the use of RWD/RWE. Discussants believed that the conversation on how to use RWE was much more theoretical in the HTA/payer space, compared to regulatory where tangible guidelines exist.

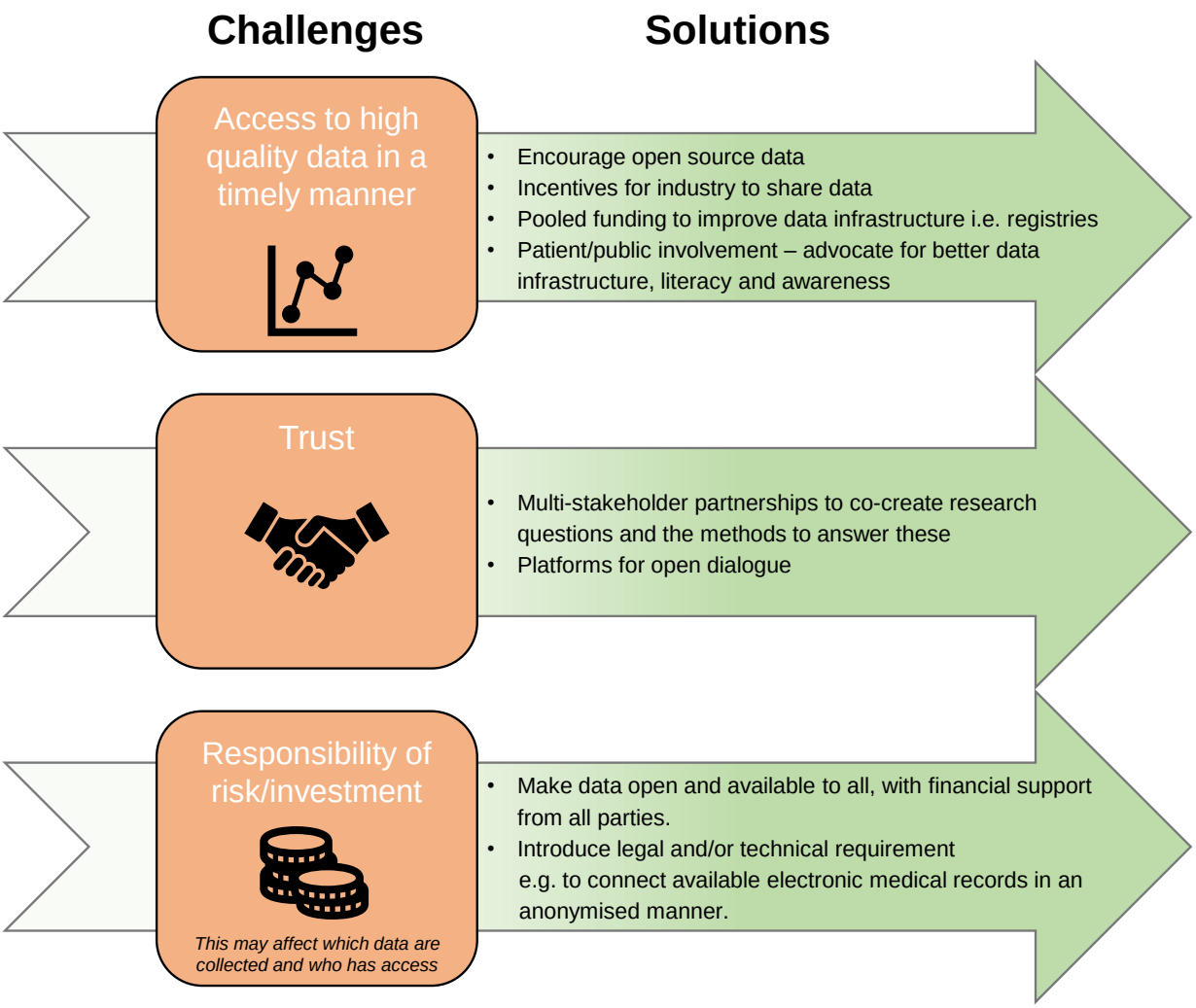
The breakout group concluded that RWD/RWE already has a role in addressing the efficacy-effectiveness gap but is not being used in a predictive process. Therefore there needs to be further work to develop the right infrastructure and tools to enable RWD/RWE to be used in this way.

Q1b. What are seen as the main areas or advantages where RWD and RWE could provide value to shape a more predictive process of "efficacy to effectiveness" assessment?

Areas/advantages	Timing during the drug life cycle	Future direction - how can this expand?
Rare diseases in terms of therapeutic area (But all therapeutic areas benefit from RWE)	Across entire drug life cycle	• Focus not on therapeutic areas but holistic picture – what questions need answering and how can RWD address those gaps?
Early advice	1. Pre-approval, where there is high confidence that an asset will move forward from early discovery into development 2. When designing the pivotal study 3. After Phase I – when determining the specific diagnosis that should be pursued	• Need more demonstration projects and concrete case studies • There must be collaboration among the companies as well as HTA agencies, payers and patients to determine what data needs to be collected and how to improve trust. • Example from Alzheimer's: early advice on RWE may have encouraged companies to work together in a pre-competitive space to develop a robust disease registry, since there was a complete lack of historical datasets.

Areas/advantages (cont.)	Timing during the drug life cycle (cont.)	Future direction - how can this expand? (cont.)
After authorisation in one indication but seeking authorisation in other indications (industry perspective) OR where drug clearly shows off-label use that is beneficial for patients/ society (payer perspective)	Post-authorisation (Where there is sufficient evidence and data leading to authorisation – already a high level of confidence in the molecule)	• Feasibility of data collection and who funds this needs to be further explored. • Consistent theme over the workshop – data quality is the current biggest challenge, nevertheless there is an opportunity for prospective evidence generation e.g. randomised pragmatic studies.
Conditional approval process	Post-authorisation	• This is well explored from the regulatory perspective.

Q2. Considering the areas or advantages identified in Q1b, what are the biggest challenges (real or perceived) to enable these to occur and what are potential solutions?



Q3. What policy changes are required to help address the challenges identified in Q2?

- Transparency and openness on data access and data sharing
- Develop guidance on what constitutes good RWE
- Ensure that there is a platform for open dialogue between stakeholders so that research questions can be developed together

Q4. Recommend future research projects for CIRS and other groups to undertake in this area – what should be considered to support or improve current activities?

1. Develop guideposts/standards around focused RWE use cases e.g. how to address the efficacy-effectiveness gap in a specific therapeutic area or situation.

Breakout discussion B

Early access medicines: optimising the use of RWE for regulatory and HTA decision making – what are the opportunities, barriers and solutions?	
Chair	**Prof Hubert Leufkens,** *Emeritus Professor, Utrecht University, The Netherlands*
Rapporteur	**Rob Kalesnik-Orszulak,** *Director, Regulatory Innovation Lead for RWE and Data Science, Bristol Myers Squibb, USA*

Background

Regulatory agencies have implemented a number of expedited processes to enable early access for medicines that focus on a high unmet need as well as to make available increasingly more technologically complex innovations being are brought through development. This means that the regulatory approval can be on early promise based on interim analysis and early data. However, for these routes and types of medicines, the evidence available on relative effectiveness and risks of new health technologies that is available for HTA at the time of a marketing authorisation application, is often limited. Data insufficiencies on treatment effects, safety and costs at the time of HTA assessment are often a concern and having good quality data is important to minimise uncertainty in reimbursement decision making.

This has led to an increased focus on the potential for utilising and enabling RWD and RWE at the time of initial decision, as well as building in post-licensing evidence generation needs, in order to have robust ways of measuring these products' promise in the real world. This is important for early access medicines as it is important to ensure an ongoing benefit-risk assessment for the regulators and relative effectiveness assessment for the HTA agencies.

The key consideration for this breakout was how to enable the active use of RWD/RWE in regulatory and HTA decisions for early access medicines; what is the current situation and how could the use of RWD and RWE be optimised so it is fit for purpose for regulatory and HTA decision making?

This breakout group was therefore asked to build on the workshop discussions and frame the group discussion around the use of RWD/RWE for early access medicines. The objectives of this breakout were to discuss:

- What are the main opportunities/advantages for incorporating RWD/RWE into decision making practices within companies, regulatory authorities and HTA agencies for development, regulatory review and HTA recommendation for early access medicines?
- What are the main challenges/limitations today to incorporating RWD/RWE into decision making practices within companies, regulatory authorities and HTA agencies for development, regulatory review and HTA recommendation?
- What needs to be considered to optimise the use of RWD/RWE in the future so that it is fit for purpose to be incorporated into decision making – what are the policy/research needs to address the key challenges?

Discussion results

Q1. What are the main opportunities/advantages for incorporating RWD/RWE into decision-making practices for early access medicines within companies, regulators, HTA agencies and payers for development, regulatory review, HTA recommendation and reimbursement?

The breakout group concluded that there were two main opportunities for incorporating RWD/RWE into decision making for early access medicines and that these were relevant to all stakeholders (companies, regulators, HTA agencies and payers):

RWE as external/hybrid controls to speed up development and shorten the time to regulatory/HTA/payer approval, particularly in cases of high unmet need and large treatment effect.

RWE in the post-market setting e.g. registries, pharmacovigilance programmes. This facilitates better understanding of the drug, as the original clinical evidence for early access medicines may be limited in certain aspects e.g. long-term effects, certain subpopulations.

Q2. What are the main challenges/limitations today to optimising the incorporation of RWD or RWE into decision making practices for early access medicines?

Q3. What solutions or policy changes are required to help address the challenges identified in Q2?

Main challenges/limitations (Q2)	Solutions or policy changes (Q3)
Stakeholder differences • Differing expectations e.g. regulators vs HTAs • Communication/terminology – lack of clarity on what is being provided under the RWE umbrella term	• Cross-stakeholder discussion to align expectations e.g. through workshops • Establish common language across stakeholders
Data relevance and reliability • Identifying data source that includes the right elements e.g. target population, outcomes • Finding data source of sufficient quality	• Development of data standards • Cataloguing of data sources

Main challenges/limitations (Q2) (cont.)	Solutions or policy changes (Q3) (cont.)
Pricing • Business considerations can influence the way in which RWE is utilised, reviewed and priced	• Cross-stakeholder discussion to facilitate alignment e.g. through workshops
Mindset / expertise gap • All stakeholders used to traditional approach and may operate on precedent • All stakeholders can lack the expertise (data sciences etc) to propose/review innovative RWE approaches	• Training • Hiring/resourcing • Collaborations with academia/experts for advice

Q4. Recommend future research projects for CIRS and other groups to undertake in this area – what should be considered to support or improve current activities?

The breakout group emphasised the need for all stakeholders to work together to overcome challenges, including the mindset/expertise gap, regulatory-HTA alignment and the development of data standards. The group recommended that CIRS and/or other groups conduct:

1. Further cross-discipline workshops
2. Corresponding research projects e.g.
    a. Assessing different data standards in terms of strengths and limitations
    b. Evaluating when and where RWE approaches have been utilised successfully and unsuccessfully – this will help to set stakeholder expectations

Breakout discussion C

Aligning RWD/E to meet regulatory and HTA needs within and across jurisdictions – how can this be best achieved?	
Chair	**Prof Anthonius de Boer,** *Chairman of the Medicines Evaluation Board, The Netherlands*
Rapporteur	**Dr Stephanie Manson,** *Senior Director, Worldwide Value and Access, Novartis, USA*

Background

RWD/RWE can bring value to every stage of a drug's life cycle. Although regulatory and HTA submissions are likely to remain focused on randomised controlled trials (RCTs) in the future, these are also likely to be supplemented with RWD/RWE as agencies and companies increasingly recognise the value of RWD/RWE.

As new medicines are brought to market utilising expedited regulatory processes and increased complexity of health technologies, is there an increased necessity of RWD as an addition to data from traditional RCTs? With these early access medicines, it is important to ensure an ongoing benefit-risk assessment for the regulators and relative effectiveness assessment for the HTA agencies. Thus, the development and alignment between companies, HTA agencies, regulators and payers in the RWD/RWE space is critical to ensure that real world studies designed by companies can, if possible, also be of value to regulatory, HTA and payer stakeholders both within and across jurisdictions. This requires collaboration between stakeholders as well as possible convergence, harmonisation or a road map regarding scientific advice and guidance on RWE generation and use.

Discussions on the generation and use of RWD/RWE have been undertaken at a regulatory level through the International Coalition of Medicines Regulatory Authorities (ICMRA). This topic has also been raised and discussed through the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), the European network for HTA (EUnetHTA) and through Innovative Medicine Initiative (IMI) projects involving both companies and agencies. In addition, a number of agencies have produced their own RWD/RWE guidelines. Although the direction of travel is for more robust RWD/RWE, it is important that guidance is not fragmented. Therefore, the key question is, what are the areas to encourage and provide alignment to ensure that real world studies and data generated is fit for purpose for decision makers?

The main consideration for this breakout was to discuss how best to align across regulatory and HTA needs both within and across jurisdictions. This breakout was therefore asked to build on the workshop discussions and frame the discussion around evaluation of new medicines. The objectives of this breakout were to discuss:

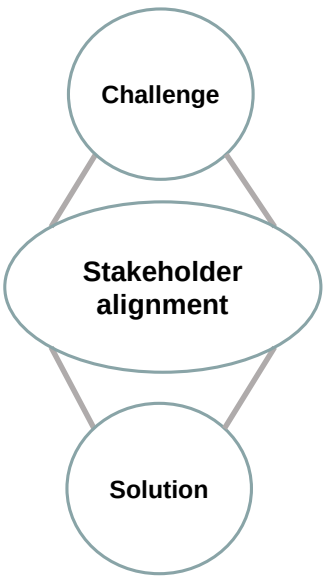
- What are the main initiatives or areas of opportunity for alignment or collaborations between companies, regulators and HTA agencies within and across jurisdiction on RWE generation - what is the current status and future direction?
- What are the current or perceived challenges to aligning RWD/RWE to meet regulatory and HTA needs within and across jurisdictions?
- How should RWE generation capabilities be reinforced and what needs to change in respect to reaching stakeholder consensus on the use of RWE to ensure it meets regulatory and HTA needs within and across jurisdictions?

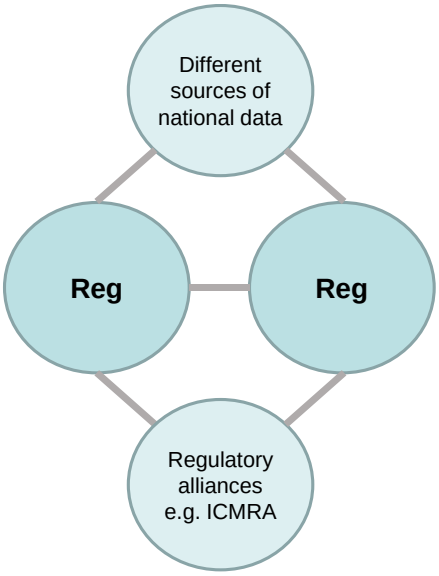
Discussion results

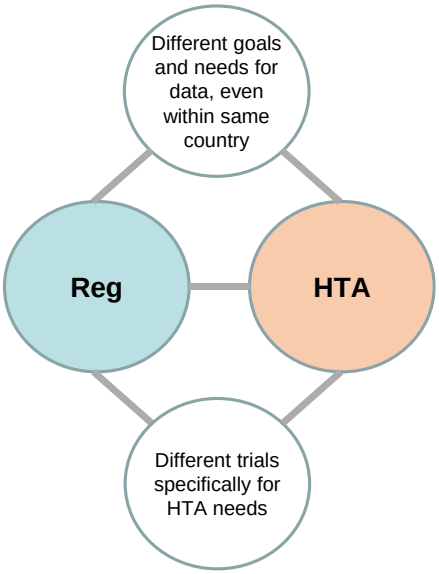
Q1. What are the main areas/initiatives for alignment activities or collaborations between companies, regulators and HTA agencies within and across jurisdiction - what is the current status and value?

Initiatives	Status and perceived value	How should these evolve?
1. IMI projects: • Get Real Institute • Adapt Smart • Trials at Home	Many initiatives providing guidelines, addressing data quality and transparency. However, there are questions around who the audience is, whether the outputs are reaching decision makers and whether these initiatives are having an impact on the quality of individual drug evaluations.	Acknowledge that there is no 'one size fits all' approach for RWE collection or application. Create and enforce universal expectations of what is necessary in terms of RWE quality
2. Regulatory information sharing e.g. through ICMRA		
3. Data networks: • Data Analysis and Real World Interrogation Network (DARWIN EU) • European Health Data Evidence Network (EHDEN)		
4. Regulatory/HTA alignment within countries e.g. Canada		
5. HTA-related initiatives: • EU HTA Regulation • ISPOR RWE Transparency Initiative		

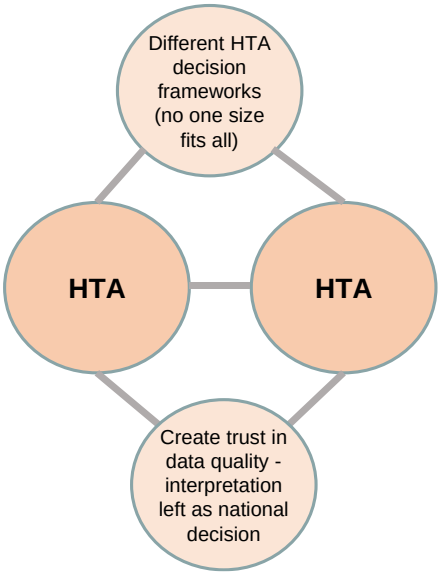
Q2. What are the current or perceived challenges to aligning RWD/RWE to meet regulatory and HTA needs within and across jurisdictions and what would be potential solutions?







Reg = Regulator
HTA = HTA agency



Q3. How should RWE generation capabilities be reinforced to enable such data generation to be of value for regulators and HTA agencies within and across jurisdictions? What needs to change to enable stakeholder consensus on RWE acceptability?

Areas for consideration **e.g. landscape, process changes, skillsets**	**Solution or policy changes required**
Even with guidelines, **issues with data quality** persist	• Better **pre-alignment** on regulatory/HTA RWE expectations • Create **incentives** for better quality RWE
There is no such thing as bad data, just **inappropriately applied data** for a question	• Need to tailor questions to **data capability** • Ensure **no 'one-size fits all' approach** for individual assessments
Change management for implementing better RWE	• Recognise that bringing all stakeholders along in the journey takes time • Need to **anticipate barriers**/issues

Q4. Recommend future research projects for CIRS and other groups to undertake in this area – what should be considered to support or improve current activities?

1. More opportunities for regulators/HTA agencies/industry to work together, not only on RWE principles but also specific applications
2. Learn and share from best practice examples of RWE application

Breakout discussion D

What framework or criteria need to be in place to ensure fit-for-purpose RWE for utilisation as part of a life cycle approach for medicines assessment by HTA and regulatory agencies?	
Chair	**Dr Álmath Spooner,** *Director, Regulatory Policy and Intelligence, AbbVie, Ireland*
Rapporteur	**Lucia D'Apote,** *Director, ELMAC Lead for Global Regulatory and R&D Policy, Amgen, UK*

Background

As new medicines are brought to market utilising expedited regulatory processes and increased complexity of health technologies, there is an increased necessity for RWD as an addition to data from traditional randomised controlled trials. However, for HTA, the evidence on relative effectiveness and risks of new health technologies that is available at the time of a marketing authorisation application is often limited. Data insufficiencies at the time of HTA assessment on real-life treatment affects safety and is often a concern. Having good quality data is important in order to minimise uncertainty in reimbursement decision making.

To help resolve uncertainties and mitigate risk at the time of initial approval has led to thinking that, for some medicines, a longitudinal or life cycle approach needs to be considered where collection of RWD would be key. With early access medicines, it is important to ensure an ongoing benefit-risk assessment for the regulators and relative effectiveness assessment for the HTA agencies.

There are a number of considerations and suggested frameworks with regard to RWD and RWE; the key consideration for this breakout group was to discuss what framework/building blocks/criteria need to be in place to ensure fit-for-purpose RWE for use as part of a life cycle approach for medicines assessment. The group was therefore asked to build on the workshop discussions and frame the discussion around evaluation of medicines.

The objectives of this breakout group were to discuss:

- What is the need for a life cycle approach framework and why would this be of value to develop?
- What are the key characteristics/domains that would need to be considered for a life cycle approach? With a focus on utilisation of RWE within such a life cycle approach framework, what are the building blocks for consideration in an effective framework?
- What are the main challenges to using RWE in a life cycle approach and what solutions/policy actions are needed to support the evolvement of a life cycle approach framework?

Discussion results

Q1. What are the key advantages/needs for a life cycle approach? Identify what this means for different stakeholders.

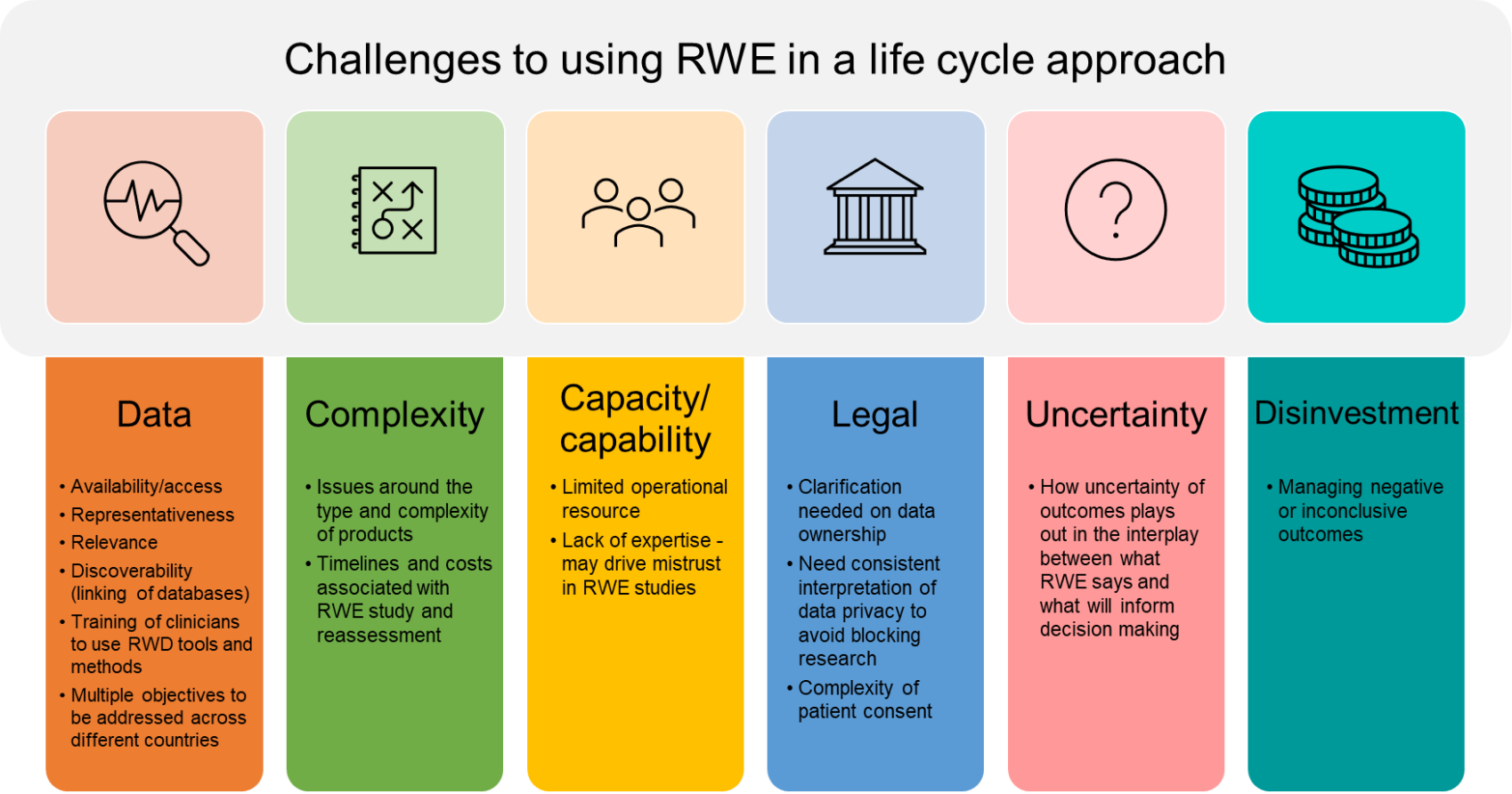
The breakout group agreed that evidence generation is a continuous process that does not stop at regulatory authorisation but continues with HTA and beyond. The key advantages of a life cycle approach are **timely patient access** to innovative treatments (also targeting smaller patient populations) and **effective use of accelerated pathways and conditional marketing authorisation**. Use of a life cycle approach gives **opportunities for a learning healthcare system, alignment between stakeholders** e.g. on RWD/RWE frameworks and guidelines, and **early dialogue between regulators, HTA agencies and payers**, which can be a tool to manage uncertainties and move to dynamic assessment of data.

Patient representatives in the breakout group highlighted the ongoing challenge to find where RWE fits into the 'evidence pyramid' that guides evidence-based medicine. For HTA agencies, a life cycle approach was deemed to already be a reality, as regulators have authorised a number of products based on RWE. Industry highlighted the benefit of having early discussions with regulators and HTA agencies, which will enhance trust on RWD/RWE and help to define research questions upfront.

Q2. What are the key characteristics/domains that would need to be considered for a life cycle approach? With a focus on utilisation of RWE within such a life cycle approach framework - what are the building blocks for consideration in an effective framework?

Framework domain	What are the key themes/building blocks that need to be built in?
Framework following the research process: • **Engagement processes** • **Data sources (relevance, reliability)** • **Study design & protocol development:** Study protocol as the cornerstone of the research process • **Analytical methods:** Validated and well described analytical methods • **Study transparency:** Transparency for the conduct and use of non-interventional studies • **Study reporting:** Reducing bias including confounding • **RWD/RWE submission** • **Final report evaluation**	• **Engagement of all stakeholders at each point of the life cycle** • **Patients are partners**: it is important to hear their perspective in designing/conduct studies. • **Legal clarification on data ownership**: consistent interpretation of data privacy, without blocking research. • **Use of patient registries**: in rare disease there can be competition to enrol patients in disease vs product-based registries. Disease registries are favoured but product registries are needed for pharmacovigilance. • **Data and digital policy infrastructure:** need to ensure that data can be shared across jurisdictions and used to generate evidence. • **Comprehensive aligned/convergent guidelines** need to be built in. • **Consolidated use of tools post marketing** - also use them more to inform pre-marketing (epidemiology, rare diseases, precision medicine, patient-focused drug development)

Q3a. What are the main challenges or limitations to using RWE in a lifecycle approach?



Q3b. What solution or policy changes need to be in place to support the use of RWE in a fit-for-purpose approach to assessment of medicine during the life cycle?

- Build a **roadmap with modular blocks and iterative collaboration** - building on experience e.g. COVID-19 pandemic, registry initiatives, single arm trials
- Leverage and better connect efforts from current **multi-stakeholder initiatives** e.g. Duke Margolis RWE Collaborative
- Leverage opportunities from **HTA Cooperation Regulation**
- **Collaborate** across different stakeholders and jurisdictions
- **Engage** all stakeholders at each point of the life cycle
- Set up **learning initiatives** - use experience to inform guidelines and international convergence
- Enhance **horizon scanning** (industry need to contribute - increase predictability from scientific advice)
- Establish a **platform to address operational barriers** - requires adaptation of the healthcare system and the HTA agency to update infrastructures and methodologies to assess RWD/RWE
- **Agree on good principles** to address possible contradicting results from different studies that answer the same question
- Consistently interpret **data privacy**
- Implement **technology solutions** to simplify data linkage, consent, data transparency, privacy and ownership e.g. individual unique identifier system

Q4. Recommend future research projects for CIRS and other groups to undertake in this area – what should be considered to support or improve current activities?

1. Connect efforts from current multi-stakeholder initiatives
2. Engage on EMA regulatory science research needs
3. Establish a process to grade uncertainty

Appendix: Workshop attendees

Affiliations are stated as they were at the time of the meeting.

Regulatory agencies		
Stiina Aarum	*Scientific Officer*	*European Medicines Agency (EMA), The Netherlands*
Majidah binti Abd Rahman	*Senior Principal Assistant Director*	*National Pharmaceutical Regulatory Agency (NPRA), Malaysia*
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Shafeena Anwar	*Pharmacist*	*National Pharmaceutical Regulatory Agency (NPRA), Malaysia*
Milagros Arangoitia Valladares	*Clinical Reviewer*	*General Directorate of Medicines, Supplies and Drugs (DIGEMID), Peru*
Dr Peter Arlett	*Head of Data Analytics and Methods Taskforce*	*European Medicines Agency (EMA), The Netherlands*
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Azri Bin Nasruddin	*Senior Principal Assistant Director*	*National Pharmaceutical Regulatory Agency (NPRA), Malaysia*
Prof dr Anthonius de Boer	*Chairman*	*Medicines Evaluation Board (MEB), The Netherlands*
Dr Claus Bolte	*Head of Sector Marketing Authorisation*	*Swissmedic*
Dr Rubina Bose	*Deputy Drugs Controller (India)*	*Central Drugs Standard Control Organisation, Ministry of Health & Family Welfare, Government of India*
Mei-Ling Chan	*Reviewer*	*Taiwan Food and Drug Administration, Chinese Taipei*
Dr John Concato	*Associate Director for Real-World Evidence, Office of Medical Policy, Center for Drug Evaluation and Research (CDER)*	*Food and Drug Administration (FDA), USA*
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Dr Harald Enzmann	*Chair, Committee for Medical Products for Human Use (CHMP)* *Section Head, European and International Affairs*	*European Medicines Agency (EMA), The Netherlands* *Federal Institute for Drugs and Medicinal Devices, Germany*
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Dr Luis Guillermo García Imia	*Specialist Preclinical and Clinical Section*	*Center for State Control of Drugs and Medical Devices (CECMED), Cuba*
Melissa Kampman	*Manager and Senior Epidemiologist, Marketed Health Products Directorate*	*Health Canada*
Yap Kian Yee	*Senior Principal Assistant Director*	*National Pharmaceutical Regulatory Agency (NPRA), Malaysia*
Rosliza binti Lajis	*Senior Principal Assistant Director/ Head of New Drug Product Section*	*National Pharmaceutical Regulatory Agency (NPRA), Malaysia*
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Dr Celia Lourenco	*Director General, Biologic and Radiopharmaceutical Drugs Directorate*	*Health Canada*
Lorraine Nolan	*Chief Executive*	*Health Products Regulatory Authority (HPRA), Ireland*
Patricia Oliveira Pereira Tagliari	*Deputy Director – Second Directorate*	*Brazilian Health Regulatory Agency (ANVISA), Brazil*
Gustavo Santos	*General Office of Medicines and Biological Products – GGMED*	*Brazilian Health Regulatory Agency (ANVISA), Brazil*
Dr Junko Sato	*Office Director, Office of International Program*	*Pharmaceuticals and Medical Devices Agency (PMDA), Japan*

Dr Anja Schiel	*Lead Methodologist/ Statistician/Team leader international HTA*	*Norwegian Medicines Agency*
Adj Prof John Skerritt	*Deputy Secretary*	*Department of Health, Australia*
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Nur Syafiah Abdul Wahid	*Principal Assistant Director*	*National Pharmaceutical Regulatory Agency (NPRA), Malaysia*

HTA agencies and payers		
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Dr Nick Crabb	*Programme Director, Scientific Affairs*	*National Institute for Health and Care Excellence (NICE), UK*
Jo De Cock	*Former CEO*	*National Institute for Health and Disability Insurance, Belgium*
Dr Daniel Erdmann	*Team Lead*	*GKV-Spitzenverband, Germany*
Dr Sebastián García Martí	*Health Technology Assessment and Economic Evaluation Department Coordinator*	*Institute for Clinical Effectiveness and Health Policy, Argentina*
Niklas Hedberg	*Chief Pharmacist*	*Dental and Pharmaceutical Benefits Agency (TLV), Sweden*
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Mei-chi Lai	*Researcher*	*Center for Drug Evaluation (CDE), Chinese Taipei*
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Iain Leslie	*Principal Health Economist*	*Scottish Medicines Consortium (SMC), UK*
Dr Andrew Mitchell	*Strategic Adviser, Evaluation, Office of Health Technology Assessment*	*Department of Health, Australia*
Dr Nicole Mittmann	*Chief Scientific Advisor and Vice President*	*Canadian Agency for Drugs and Technologies in Health (CADTH)*
Dr Detlev Parow	*Former Head of Pharmaceutical Department*	*DAK-Gesundheit, Germany*
Dr Foo Sze-Shir	*Senior Principal Assistant Director*	*Ministry of Health, Malaysia*

Pharmaceutical companies and consultancies		
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Ginny Beakes-Read	*Executive Director GRR&D Policy*	*Amgen, USA*
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Celine Bourguignon	*Head of Regulatory Policy Greater China Intercontinental & Emerging Markets*	*GlaxoSmithKline, Belgium*
Frederico Calado	*Head RWE Innovation & Partnerships*	*Novartis Oncology, Switzerland*
Stephanie Chen	*Senior Specialist, AP Regulatory Policy*	*MSD, Singapore*
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Dr Sannie Chong	*APAC Regulatory Policy Lead*	*F. Hoffmann La Roche, Singapore*

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Ana Cibrian	*Global Regulatory Policy Director*	*Bristol-Myers Squibb, USA*
Francesca Cipolli	*Associate Director – GRS Precision Medicine and CDx*	*Bristol-Myers Squibb, Switzerland*
Dr Solange Corriol-Rohou	*Senior Global Policy Director*	*AstraZeneca, France*
Dr Gracy Crane	*International Policy Lead (RWD)*	*F. Hoffmann La Roche, UK*
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Dr Helen Fitton	*Senior Vice President, Regulatory Affairs*	*GlaxoSmithKline, UK*
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Dr Louise Gill	*Vice President, Regulatory Policy*	*GlaxoSmithKline, UK*
Dr Melinda Goodall	*Director – HTA Policy*	*MSD, UK*
Dr John Graham	*SVP, Head Value Evidence & Outcomes (VEO)*	*GlaxoSmithKline, USA*
Adrian Griffin	*Vice President, HTA & Reimbursement Policy*	*Johnson & Johnson, UK*
Sebastien Guerinet	*Senior Director Regulatory Affairs International*	*BridgeBio, UK*
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Georgette Kokinda	*Director, Oncology Team Lead*	*Takeda, USA*
Dr Nafsika Kronidou	*Global Regulatory Franchise Head for Breast/Gyn/ GI cancers*	*F. Hoffmann La Roche, Switzerland*
Prof Thomas Kuhler	*Head Global Regulatory Science & Policy EU/AMEE*	*Sanofi, France*
Nathalie Largeron	*Global Head of HTA Strategy*	*Sanofi, France*
Sang Mi Lee	*Access Lead, Personalized Healthcare, CGP, and Tumor Agnostic Portfolio*	*Hoffmann-La Roche, Canada*
Carol Lin	*Regulatory Affairs Senior Manager*	*Astellas, The Netherlands*
Dr Thomas Lönngren	*Independent Strategy Advisor*	*PharmaExec Consulting Filial SE, Sweden*
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Claire Martin	*Global Policy Lead*	*Bayer, Germany*
Maria Mata Lorenzo	*Associate Director HEOR Est-markets*	*Astellas, UK*
Dr Marsha Miller	*Executive Director, Regulatory Affairs*	*Bristol-Myers Squibb, USA*
Michael Muña	*Senior Director, Global R&D and Regulatory Policy*	*BioMarin Pharmaceuticals, USA*
Ruth Nasr	*Head of Market Access, EMEA*	*BridgeBio, Switzerland*
Katie Nelson	*Associate Director, Outcomes Research*	*MSD, USA*
Dr Julie O'Brien	*Director, Global Regulatory Policy*	*Pfizer, Ireland*
Claudia Popp	*Head EU Regulatory Science & EMA Liaison*	*F. Hoffmann La Roche, Switzerland*
Brandy Proctor	*Regulatory Policy Manager*	*GlaxoSmithKline, USA*
Dr Tomas Salmonson	*Director*	*Consilium Salmonson & Hemmings, Sweden*
Susan Sandler	*Director, EMEA Policy, Global Regulatory Policy and Intelligence*	*Janssen, USA*
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