ECONOMIST IMPACT

Value of Real-World Evidence in Health Technology Assessment: lost in translation?

Supported by Roche

Contents

About this report

The white paper *"Value of Real-World Evidence in Health Technology Assessment: lost in translation?"* is an Economist Impact report, sponsored by Roche. The report explores the value that Real-World Evidence (RWE) can add for assessing relative treatment effects during the first Health Technology Assessment (HTA) of innovative new medicines. It also explores key barriers to increased use of RWE and, informed by current initiatives and views of experts, prospects for the future. RWE is evidence derived from the result of analysis of Real-World Data (RWD). Definitions of RWD vary, RWD is often defined as data that is collected outside of a randomised controlled trial setting.[1]

We focus specifically on how RWE can be used to inform decisions on relative treatment effects. This is because many therapies are coming to market for rare diseases or highly targeted patient populations where there are small patient numbers—randomised controlled trials (RCTs) are difficult to do in these instances for practical and ethical reasons.[2] How can RWE add evidence against this backdrop?

We thank the following experts who took part in interviews to support this research:

- **Professor Isabelle Durand-Zaleski**, Université de Paris, CRESS, INSERM, INRA, URCEco, AP-HP, Hôpital de l'Hôtel-Dieu;
- **Don Husereau**, Adjunct professor, University of Ottawa, School of Epidemiology and Public Health;
- **Alastair Kent**, OBE, Consultant in Health Policy and Patient Engagement in Rare and Genetic Diseases;
- **Professor Gillian Leng**, CBE, healthcare adviser and international guidelines expert;
- **Durhane Wong-Rieger**, President and CEO, Canadian Organization for Rare Disorders

Their participation in interviews does not imply endorsement of the report. The views of interviewees were their own and not necessarily those of their affiliated institutions. Economist Impact bears sole responsibility for the content of this report. The findings and views expressed in the report do not necessarily reflect the views of the sponsor, Roche.

The Economist Impact research team consisted of Rob Cook, Alan Lovell, Aanisah Khanzada, and Leela Barham, with additional support from Kritika Rai. All best efforts were used in conducting the research for this report, but any interpretation or transposition errors are due to human error. Economist Impact cannot accept any responsibility or liability for reliance by any person on this report or any of the information, opinions or conclusions set out in this report.

Executive summary

Real-World Evidence for therapeutic assessment is back on the agenda

Real-World Evidence (RWE)—derived from Real-World Data (RWD) collected outside of randomized controlled trials—has played a role in health care for hundreds of years, even if the term itself has been coined more recently.

The use of RWE on the relative treatment effects of new therapies in the context of Health Technology Assessment (HTA) is a hot topic. In part, this is because RWE is increasingly accessible and the methods to analyze it have improved. It is also because many treatments, for practical or ethical reasons, are coming to market just with evidence from single-arm trials—where everyone in the trial gets the same medicine and there is no comparator. RWE can complement evidence from these trials. However, there remains concerns about bias in RWE.

However, its use in Health Technology Assessment remains limited

We have assessed how RWE is valued in the assessment of treatment effectiveness in the HTA of eight therapies (Kymriah, Luxturna, Tecartus, Yescarta, Zolgensma, Evrysdi, Polivy and Rozlytrek). These are all complex therapies, where trials can be challenging to conduct, and hence RWE is likely to add value.

We looked at initial HTA reports from five mature HTA agencies in Australia, Canada, England, France, and Germany. RWE was used in particular for the effectiveness of the comparator, helping to plug gaps in the clinical trial evidence, but also, more rarely for the effectiveness of treatment. Agencies in England (NICE) and Canada (CADTH) were most likely to use RWE.

For only two of the eight therapies (Evrysdi and Zolgensma) was any positive language found in one or more final HTA reports about the impact of RWE for decision making. More often than not, RWE was either not cited, considered but disregarded, or discussed but in a neutral or ambiguous manner.

We also found that HTA agencies used inconsistent terminology, with different terms for the same type of evidence. That is confusing. It is also sometimes unclear why an agency may have accepted or disregarded RWE. When reasons for disregarding RWE were given, they included patient heterogeneity, concern about bias, and a preference for homegrown RWE. Oftentimes, there is a sense that there is more that is left unsaid in the HTA report. Our research holds up a mirror to HTA agencies and, right now, agencies are not transparent enough about their use of RWE.

Institutional barriers, and a lack of transparency, block its greater use

Yet there is a reason for optimism about making the most of RWE in HTA in the future

for assessing relative treatment effects. Many in the HTA community are pragmatic and recognize that RWE can complement trial data. Institutional barriers exist, but they are not insurmountable. Barriers to overcome include a lack of consistent terminology across HTA agencies, which can confuse stakeholders. A lack of early engagement on the potential to use RWE, as well as a lack of clear guidance from HTA agencies. Finally, a lack of evidence and transparency means that stakeholders are often uncertain what impact RWE has on HTA decision-making.

Five steps to overcome the "consistently inconsistent" use of Real-World Evidence in decision making

What is most striking is how consistently inconsistent the use of RWE is in HTA. HTA agencies will need to help those who play a role in producing RWE, so that they can produce the type of RWE agencies are looking for. Five practical steps can be taken to realize more value from RWE in HTA for relative treatment effects:

- **HTA agencies should declare a greater openness to the use of RWE.** As a first step, they could review their industry guidance documents to explore how to make openness to RWE more explicit.
- **HTA agencies and the industry need to develop a shared terminology.** This could mean adopting and using a pre-existing glossary of terms, adapting these as necessary over time.
- **Early engagement and collaboration between HTA agencies and industry on the potential use of RWE for relative treatment effects should be normalised.** HTA agencies and industry should consider adding RWE as a standing agenda item during early engagement discussions
- **HTAs should promote transparency in their use of RWE to support the development of an evidence base.** HTA agencies could add a section in their final decision documents for a discussion of their use of—or why, if it is disregarded—RWE for the final assessment decision.
- **As RWE continues to evolve, expertise within agencies needs to be maintained and promoted throughout the agency.** Technical teams in HTAs should have as part of their role the dissemination of RWE expertise throughout the agency as a whole.

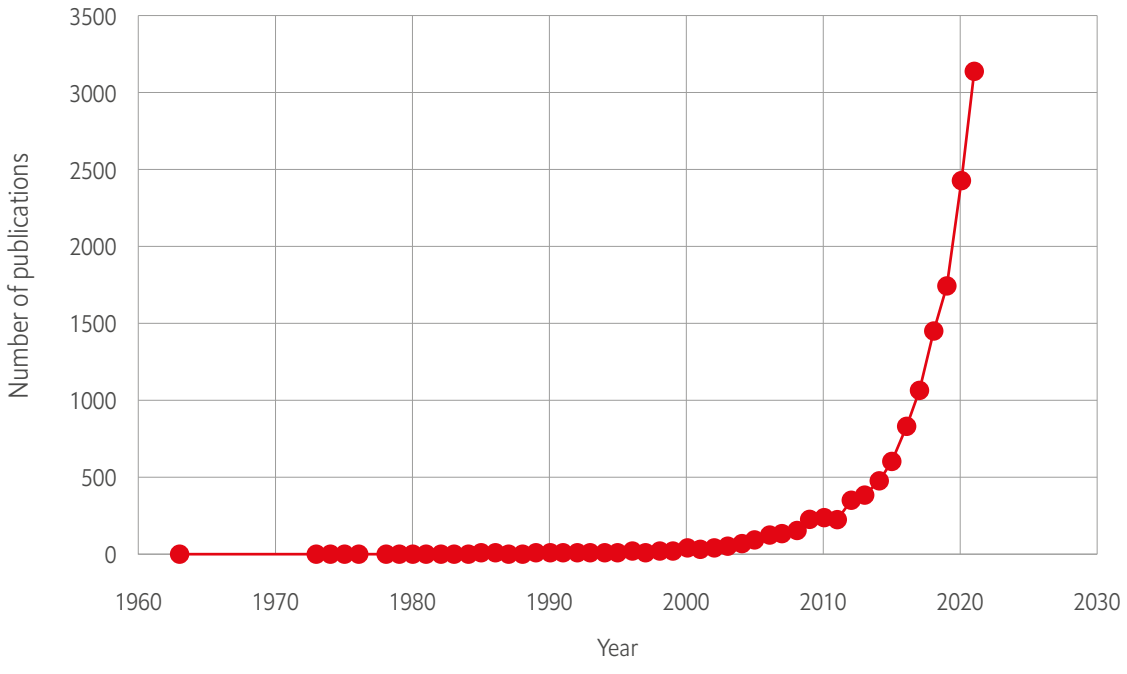
Introduction

A renewed interest in old data sources

Using Real-World Data (RWD) to create Real-World Evidence (RWE) is not new in health care. Florence Nightingale, the English statistician and founder of modern nursing, played a key role in bringing statistics into health care, calling for uniform collection of hospital statistics during the 1860 International Statistical Congress.[3] In part, this was because hospital medical records—a type of RWD that is still used today to produce RWE, even if it wasn't called that at the time —weren't fit for use.

Interest in RWE has exploded in recent years. As a proxy indicator, literature with the term Real-World Evidence first appeared in 1963 but hit a peak of over 3,000 papers in 2021 **(Figure 1)**. Recent interest in the use of RWE has been driven by several factors. Advances such as electronic medical records have made RWD more accessible and useful.[4] The rigour of methods applied to RWD has also improved,[5] although there remain concerns about potential biases due to lack of randomization, data quality, and the chance of spurious results arising from data mining.[6]

FIGURE 1: Published literature including the term 'Real-World Evidence' over time



Source: Data from PUBMED search on Real-World Evidence run on 25 May 2022.

Whilst there is widespread interest in the use of RWE in health care generally, there is relatively less focus on its use in Health Technology Assessment[1] (HTA) and, in particular, its use for assessing relative treatment effects. For example, a European mapping exercise published in 2021, found that of 192 initiatives in RWD for research, clinical care, regulatory decision-making, HTA and policy-making, just 11 (6%) were focused on HTA.[7]

Real-World Evidence for the assessment of relative treatment effects is increasingly relevant for HTA given the rise of single-arm trials for regulatory approval

There are many ways that RWE can be used in HTA. England's HTA agency, the National Institute for Health and Care Excellence (NICE), has described a variety of well-established methods in which RWD is utilised. These include characterizing health conditions, in economic models, and assessing the applicability of clinical trials to patients in the UK.[8] However, one area where there is debate is the use of RWE to inform analysis and judgement of relative treatment effects in the initial assessment of innovative medicines.[2]

This is an area of interest because many more treatments are coming to market for rare diseases or highly targeted patient populations. In these settings, small patient populations and ethics will influence the trials that can be conducted. Clinical trials will not always be possible to cover, for example, life-long effects, and it may not be ethical to randomise patients to a control group. When trial evidence is limited, sufficient quality and quantity of data on treatment effects, safety and costs may not be available at the time of a HTA assessment. Although evidence can build over time, for example through requirements set by regulators for long-term safety.

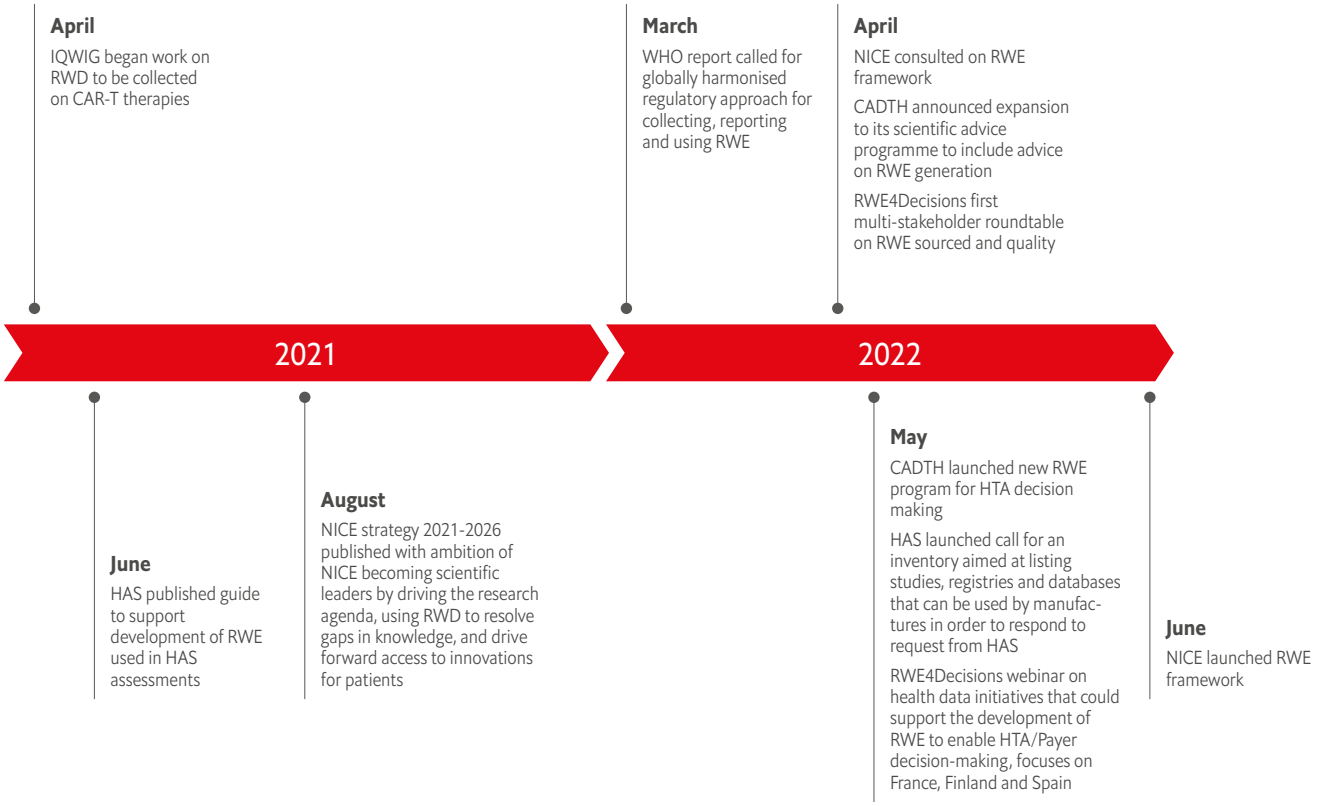
Limited evidence at the time for the first HTA is particularly the case for complex therapies or those that have been expedited through the regulatory process.[9] There is interest in how different types of RWD and how RWE can add evidence against this backdrop.[2]

Single-arm trials—where everyone in the trial gets the medicine and there is no control group of people with a similar condition who don't get the medicine—are increasingly being accepted by regulators in a bid to speed up approval of treatments in areas of high unmet need.[2] Single-arm trials used for US Food and Drug Administration (FDA) approvals have been credited with allowing rapid advancement in cancer drug development.[10] However, such trials have a corresponding impact on the evidence available for a subsequent HTA, and as such has led to a trend toward Real-World Data external comparators.[2]

However, despite its increasing importance, guidance on the use of RWE to inform HTA on relative treatment effects has little coverage of single-arm studies and in many cases, the guidance is fragmented and covered in separate documents from the same HTA agency.[11] There is a concern that differences in guidance from HTA agencies may have been discouraging the use of RWE.[12]

1 HTA is as a multidisciplinary process that determines the value of a health technology. HTA can be done at different points in time over a technology's life cycle. The aim of HTA is to inform decision-making to contribute to equitable, efficient and high-quality health systems.6 There are different models used for HTA but, importantly, they all at heart include a comparison of the new treatment compared to an alternative.
2 Whilst not the focus of this White Paper, RWE can also be used in later re-assessments.

FIGURE 2: Recent RWE initiatives linked to HTA



People working in HTA are keen to promote use of Real-World Evidence, but institutional barriers remain

But there is progress. Initiatives on RWE in HTA now abound, with ongoing work by groups like the GetReal Institute[13] in Europe as well as international work such as a new International Society for Pharmacoeconomics and Outcomes Research (ISPOR) microsite on RWE.[14]

HTA agencies too are taking forward their work on RWE. For example, the National Institute for Health and Care Excellence (NICE) published its final RWE framework on 23 June 2022 (published after the research for this paper was conducted). The RWE framework forms part of the work of NICE to deliver on their strategy and ambition to use "RWD to solve gaps in knowledge as well as drive forward access to innovations for patients."[15] The NICE RWE framework focuses on the planning, conduct and reporting of RWD. There have been a number of other RWE initiatives from other HTA agencies over the last 18 months **(Figure 2)**.[16-23]

There is a feeling too, amongst our interviewees, that RWE will play an increasingly central role in HTA in the future. "Engagement with the patient and their community, the willingness to generate additional data, to demonstrate the clinical added value of the intervention, to demonstrate the ability of that intervention to lessen the burden of the disease, is important now, but it's going to be increasingly important in the future," explained Alastair Kent, Consultant in Health Policy and Patient Engagement in Rare and Genetic Diseases.

Professor Gillian Leng, healthcare adviser and international guidelines expert, agreed, adding, "I'm fairly hopeful that we will be able to use RWE confidently to give us a robust answer [in HTA]."

Report objectives

Against this backdrop of greater interest in RWE to help explore relative treatment effects in HTA, the goals of this report are to:

1. Assess the value of RWE to inform assessment of relative treatment effects by reviewing the first HTA reports for eight treatments where RWE would be likely to complement the existing clinical evidence base, across five mature HTA agencies
2. Address key barriers to the increased use of RWE for assessing relative treatment effects during HTA
3. Take stock of current initiatives and expert views on using RWE in HTA

We conclude the report with identifying key principles around which efforts can be made to further expand and improve the use of RWE in HTA.

Assessing the value of Real-World Evidence in HTA

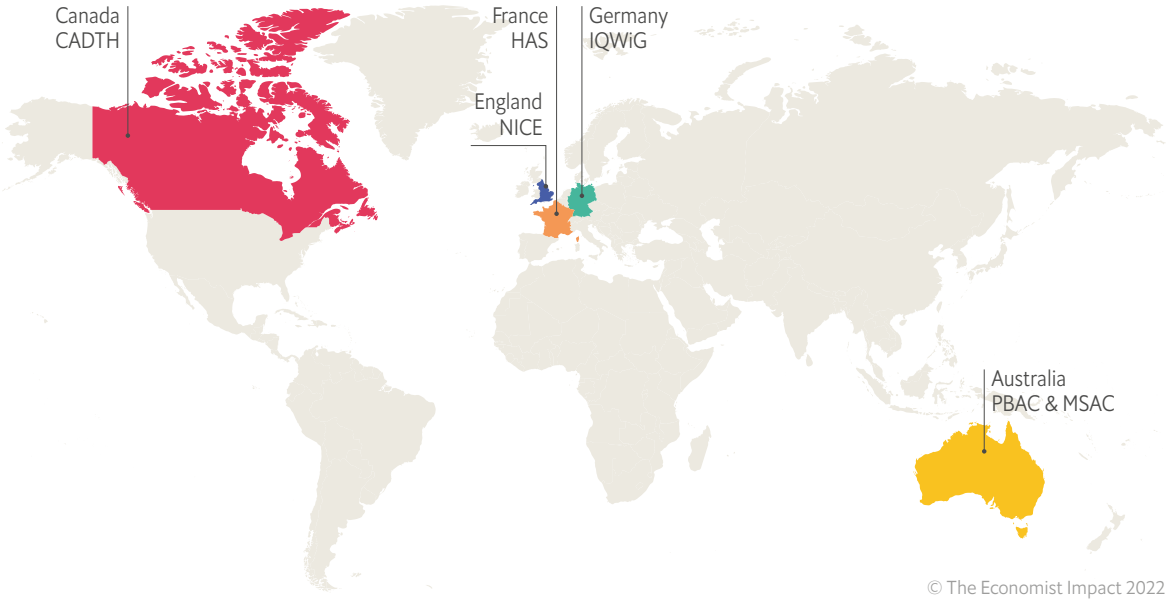
An investigation of real-life decision making

To understand what value HTA agencies have placed on RWE in judging the relative treatment effects of innovative medicines we reviewed the first HTA report on eight therapies from the following agencies:

1. **Australia** (Pharmaceutical Benefits Advisory Committee (PBAC), the Medical Services Advisory Committee (MSAC))
2. **Canada** (Canadian Agency for Drugs and Technologies in Health (CADTH))
3. **France** (Haute Autorité de santé (HAS))
4. **Germany** (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG))
5. **England** (The National Institute for Health and Care Excellence (NICE))

HTA systems vary across these countries, in terms of how they are set up, their role, and how funding decisions are reached.[24] Our research did not look at all the agencies that may consider RWE to inform access decisions. For example, it did not look at reports from Geimeinsamer Bundesausschuss (G-BA, the Federal Joint Committee) who make final decisions in Germany on the added benefit of a new treatment. The G-BA are often, but not always, informed by a report on benefit assessment from IQWiG.

For each agency we investigated (where data was available) how RWE was used for the first assessment of eight therapies: five Advanced Therapy Medicinal Products (ATMPs) and three therapies that had gone through the PRIME programme at the European Medicines Agency (EMA). We did not look at re-assessments.



Further details about the methods can be found in **Appendix 1**.

ATMPs are medicines based on genes, tissues or cells and are considered to be groundbreaking.[25] The ATMPs in our analysis were:

- **Kymriah** (Novartis)
- **Luxturna** (Novartis)
- **Tecartus** (Kite)
- **Yescarta** (Kite)
- **Zolgensma** (Novartis)

We also looked at three treatments that had gone through the PRIME programme at EMA, a programme that seeks to speed up regulatory evaluation.[26] These were:

- **Evrysdi** (Roche)
- **Polivy** (Genentech/Roche)
- **Rozlytrek** (Roche)

Real-World Evidence is used, but inconsistently

We found that RWE was cited to inform relative treatment effects in 21 of the 34 HTAs. Overall, HTAs in Canada and England had the highest proportion of the available HTAs that reported RWE as part of their main HTA reports **(Table 1)**. They also seemed the most open of the agencies to using RWE. Evidence tables for each therapy can be found in **Appendix 2**.

RWE was most often used for effectiveness of the comparator (17 of the 21 HTAs using RWE). This is where RWE is used to provide evidence on outcomes from the comparator treatment in order to compare to the data outcomes from the new treatment. This would be particularly relevant where the main clinical trial evidence comes from single arm trials. RWE was less often used for evidence on the effectiveness of the treatment (4 of the 21 HTAs). This is where RWE may provide further insights, such as extrapolating from the clinical trial results.

RWE was described in a variety of ways by HTA agencies. That means that the same types of studies can be described by the HTA agencies in different ways and that the terms used are not mutually exclusive. We have not sought to overlay a coherent and consistent categorisation of the RWD and RWE but rather just hold up a mirror to what is published by the HTA agencies.

The HTA reports included reference to:

- Retrospective studies (4 HTAs);
- Healthcare databases (4 HTAs);
- Chart reviews (4 HTAs);
- Natural history study (3 HTAs);
- Observational studies (3 HTAs).
- Early access programmes (2 HTAs);
- Real-life/real world setting studies (2 HTAs);
- Cohort study (1 HTA);
- Longitudinal studies (1 HTA); and
- Retrospective observational studies (1 HTA).

There is clearly no globally agreed RWE taxonomy in use. This variation in terminology and overlap in study types did make identifying RWE quite challenging. And there remains fuzzy boundaries on what is and what is not RWE.

TABLE 1: Use of RWE found in HTAs of eight treatments, in Australia, Canada, England, France, and Germany

	Australia	Canada	England	France	Germany
Use of RWE in HTA	38% (3/8)	75% (6/8)	75% (6/8)	71% (5/7)	33% (1/3)

Source: Economist Impact analysis of publicly available HTA reports. Note: A first HTA report was not found in the public domain for Yescarta in France. An added benefit assessment is not conducted by IQWIG in Germany for treatments designated as orphans where the budget impact is forecast to be below EUR50million. IQWIG conducted three benefit assessments for Evrysdi, Rozlytrek and Zolgensma.

For example, we have included a case report for Luxturna (as evidence of effectiveness) in France. We have also included a Matching-Adjusted Indirect Comparison for Tecartus in Canada. This is a form of indirect comparison from across two or more trials. We included it as the comparator data were from nine "uncontrolled, mainly retrospective, open-label studies". In these instances we were following the recommendations of the RWE Navigator from GetReal.[3] Others may decide not to include such evidence.

Final recommendations varied across HTAs and therapies (**Table 2**). While more therapies that presented RWE were accepted than therapies that did not, it is not appropriate to infer from this that the presentation of RWE was a driver of higher acceptance rates. As we will see from our analysis, even in cases where a positive HTA decision was made, the RWE may have been disregarded. Also our list of therapies was not selected to be representative, but rather focus on drugs where there is a reasonable expectation that RWE was likely to be used. Therefore we cannot generalise from this table to all therapies.

TABLE 2: Recommendations from the HTA assessment of eight treatments, in Australia, Canada, England, France, and Germany

	HTAs where RWE was cited (n=21)		HTAs where RWE was not cited (n=13)	
Recommendation type	**n**	**Therapy and HTA agency**	**n**	**Therapy and HTA agency**
Positive	5 (24%)	• Evrysdi in France • Kymriah in France • Luxturna in France • Tecartus in Australia and France	1 (8%)	• Rozlytrek in Australia
Restricted	1 (5%)	• Zolgensma in France	1 (8%)	• Evrysdi in Germany
Conditional	14 (66%)	• Evrysdi in Canada and England • Kymriah in England • Luxturna in Canada and England • Polivy in Canada • Tecartus in Canada and England • Yescarta in Australia, Canada and England • Zolgensma in Australia, Canada and England	6 (46%)	• Kymriah in Australia and Canada • Luxturna in Australia • Polivy in England • Rozlytrek in Canada and England
Restricted and conditional	-		1 (8%)	• Evrysdi in Australia
Negative	1 (5%)	• Rozyltrek in Germany	4 (30%)	• Polivy in Australia and France • Rozlytrek in France • Zolgensma in Germany

Source: Economist Impact analysis of publicly available HTA reports. Note: A first HTA report was not found for Yescarta in France. An added benefit assessment is not conducted by IQWIG in Germany for treatments designated as orphans where the budget impact is forecast to be below EUR50million. IQWIG conducted three benefit assessments for Evrysdi, Rozlytrek and Zolgensma. Conditional can mean, for example, that a HTA agency recommends use subject to price discussions. Restricted can mean, for example, use within a particular subgroup of patients.

3 See RWE Navigator. Generating Real-World Evidence. Available from: https://rwe-navigator.eu/use-real-world-evidence/generate-real-world-evidence/

It can be unclear why Real-World Evidence might have been accepted or disregarded

There is acknowledgement in some HTA reports that RWE may be needed to complement clinical trial evidence. For example, in the case of Tecartus, the Australian HTA stated that, "MSAC agreed with the applicant [...] an RCT would never be feasible due to the low incidence of R/R MCL [relapsed or remitting mantel cell lymphoma] and the fact that the disease is rapidly fatal." The HTA, drew upon (what the HTA described as) chart reviews and a retrospective observational study to provide data on the effectiveness of the comparator treatment, given the main clinical trial available was a single-arm trial. Indeed, in all four of the HTAs conducted on Tecartus—in Australia, Canada, England, and France—RWE was used as a comparator (IQWIG did not conduct a benefit assessment in the case of this orphan treatment). However, even in this case, of where there was no alternative, the RWE was mostly ignored or disregarded.

In fact, only for two of the eight drugs was there relatively unambiguous language in at least one HTA report about the usefulness of the RWE evidence component (**Table 3**). This was the case for Evrysdi in Canada and England (e.g. "The committee was encouraged by early results [...] and agreed to take this into account when making its recommendations"), and Zolgensma in Australia, Canada, England, and France (e.g. The committee [...] agreed that, in the absence of a more suitable data source, it would use NeuroNext in its decision making.).[4]

TABLE 3: Impact of RWE on HTA recommendation for eight therapies in Australia, Canada, England, France, and Germany

	Australia	Canada	England	France	Germany
Evrysdi	⚪	🟢	🟢	🟡	⚪
Kymriah	⚪	⚪	🟡	🔴	⚪
Luxturna	⚪	🔴	🟡	🟡	⚪
Polivy	⚪	🟡	⚪	⚪	⚪
Rozlytrek	⚪	⚪	⚪	⚪	🔴
Tecartus	🟡	🔴	🟡	🔴	⚪
Yescarta	🟡	🟡	🟡	⚪	⚪
Zolgensma	🟢	🟢	🟢	🟢	⚪

Key: 🟢 (green) language used in the HTA report interpreted as acknowledging the usefulness of RWE in the final first assessment. 🟡 (amber) RWE was acknowledged but it was unclear how or whether it was used. 🔴 (red) RWE was considered and disregarded. ⚪ (grey) RWE evidence was not found, potentially because it was not submitted or it was, but was not mentioned in the final first HTA report. See appendix 2 and main text for more details.

Source: Economist Impact analysis of publicly available HTA reports. Note: A first HTA report was not found in the public domain for Yescarta in France. A benefit assessment is not conducted by IQWIG in Germany for treatments designated as orphans where the budget impact is forecast to be below EUR50million. IQWIG conducted three benefit assessments for Evrysdi, Rozlytrek and Zolgensma.

4 We note that assessing the impact of the RWE on decision-making by HTA agencies is the most subjective element of the analysis and other researchers may interpret the results differently.

The views of agencies on the value of RWE vary from assessment to assessment—such as cases where the same RWE has been accepted by some agencies, but disregarded by other agencies. For example, in the case of Evrysdi, RWE was used in HTAs in Canada, England, and France. There is some commonality in the descriptions provided suggesting that there was a common view that the RWE could add value. In Canada, there is a reference to how, after 12 months, 29.3% of patients who received Evrysdi were able to sit without support compared with the natural history threshold of 5%. The same text is also included in the NICE HTA. However, this is not seen in the HTA in France. Also, the source of the natural history data is unclear.

Often it is also unclear why RWE was disregarded. Using the example of Tecartus, the HTA in Australia identifies several retrospective studies. The HTA in Canada also discusses the identification of nine retrospective studies (which are not specified but seem likely to overlap with those cited in Australia). The French HTA cites SCHOLAR-2 but does not discuss other studies. The HTA by NICE cites retrospective studies on salvage therapy, including McCulloch et al (2020). This is one of the studies cited by the HTA in Australia. The RWE doesn't, however, seem to have been included in the final deliberations in Canada and France. It is unclear why it was disregarded by Canada and France, while being considered (even if its final impact on decision making is unclear) by Australia and England.

This lack of transparency means that is hard to conclude why RWE is used or not. However, at times there are hints—or occasionally clear statements made—in the final decision document on the reason for the use, or not, of RWE.

Reasons for disregarding RWE #1: Differences in patient population

One of the advantages of RWE is that it is more likely to relate to a more realistic, day-to-day, patient population than those found in randomised controlled trials—which tend to have strict inclusion criteria. However, sometimes RWE is rejected because its patient population is not sufficiently similar or it cannot be demonstrated to be sufficiently similar to the patient population being considered by the HTA. Determining similarity between clinical trial patients and those included in RWD is not always straight forward to determine. For example, there can be differences in what data is collected in trials, versus in everyday clinical practice.

The case of Yescarta illustrate the concerns HTAs have of patient heterogeneity. In Australia and England, the HTA reports refer to the SCHOLAR-1 study. SCHOLAR-1 was a retrospective, patient-level pooled analysis funded by the company to evaluate survival and response rates. Each agency had different views on SCHOLAR-1. In the Australian HTA commentary, differences between the main trial patient population and that in SCHOLAR-1 is highlighted.

The HTA in England also focussed on the heterogeneity in patients, suggesting that patients in SCHOLAR-1 had a lower burden of disease than those who would be likely to be treated with Yescarta in England.

Reasons for disregarding RWE #2: Concern of bias

HTA agencies are also concerned about bias in RWE. There can be questions raised about the degree to which this can be addressed given the RWD and the methods used to analyse it. For example, IQWIG did not consider RWE available for Rozyltrek to be "suitable for benefit assessment." The RWE was a propensity score analysis of overall survival and progression-free survival from a cohort of 69 patients treated with comparator Xalkori (crizotinib) available from the US Flatiron database. IQWIGs concerns stem from a lack of randomization and the possibility of systematic bias. RWE was not identified in the HTAs of Rozyltrek by the other country's HTAs.

Another example is that of Kymriah. While HTAs in England and France both used RWE, in the French HTA, it was noted that the company did not take RWE from pooled SCHOLAR-1 data into account, on the basis that it was a meta-analysis of clinical trials and observational studies. HAS discusses the results of SCHOLAR-1 in terms of the effect of salvage treatment but highlights many limitations with the RWE, including the inability to adjust for all relevant characteristics and missing data on response and survival.

Reasons for disregarding RWE #3: Geographic relevancy

Although not always made explicit, some HTA agencies report a concern that RWE is from a different geographic region, and therefore not applicable—and that they would prioritise RWE from their country's population. NICE, for example, has a general preference for data relating directly to the UK population that reflects current care in the NHS. That said, the potential value of international data is recognised where limited information is available.[27]

For the most part, RWE from different jurisdictions is used in HTAs. For example, in the HTA of Tecartus in Australia, RWE derived from Germany, Poland, Ireland, South Korea, the UK and the US was cited. However, there was a preference for home-grown RWE, as MSAC highlighted a lack of real-world Australian data.

Reasons for disregarding RWE #4: All of the above

There have also been times when HTA agencies make it explicit that they do not see any value at all from submitted RWE, for a whole range of reasons. For example, the HTA of Kymriah by HAS in France includes a discussion of a retrospective study and observational studies that informed an indirect comparison but which were included for "illustrative purposes only." HAS stated that "no reliable estimate of the difference in the effect of this medicine compared to current management can be made." The agency highlighted many issues that led to this conclusion, including; no systematic analysis of the differential biases of the observational studies, different durations of follow-up, different characteristics of the patients and their disease, proportions of relapsed and refractory patients, history of treatment, and the number of lines of treatment compared to the available trial data.

Barriers and opportunities

The opportunity: RWE is increasingly accepted in principle as a viable tool to use in assessing the relative treatment effects of therapies

The use of RWE as a comparator arm is increasingly recognized. "The RCT is the ideal way of looking at new medicines if we possibly can. But there is the option for RWD [at NICE], even with all the cautions and the caveats", says Professor Leng. "RWD can fill gaps. There are really two scenarios. Where there is a trial that might have limitations, like limited follow up. Then there's where there is no trial. In the absence of a trial, RWD gives us something that we otherwise wouldn't have."

"The RCT is the ideal way of looking at new medicines if we possibly can. But there is the option for RWD [at NICE], even with all the cautions and the caveats."

Professor Gillian Leng CBE, healthcare adviser and international guidelines expert

Professor Isabelle Durand-Zaleski Université de Paris, CRESS, INSERM, INRA agrees, adding, "If you're talking about internal validity then nothing is better than an RCT. If you cannot do an RCT, then clearly, the only solution is to look for other sorts of data. And in the absence of a comparator arm [in a trial], I think it would be difficult to demonstrate anything. For external validity, it is quite the opposite and RWE is very valuable."

However, HTA agencies take different approaches, but it is unclear why

While RWE was acknowledged and discussed (even if, in half the cases, finally disregarded) by all HTA agencies in the assessment of Tecartus, there are also examples where RWE was only noted by one of the agencies. In the case of Polivy, for example, RWE was only cited in the HTA in Canada (data from a cohort ATU in France was not yet available). Similarly, for Rozlytrek, RWE was cited in the HTA in Germany but not identified in any of the other HTAs from the other countries.

It is unclear what is driving this difference. For example, it's unclear whether the RWE would have been available to the companies at a time when it could be used to support HTAs carried out in different countries at different times. Timing of marketing authorisation differs across the jurisdictions, as does the speed at which a HTA follows that marketing authorisation.

It's also unclear whether companies, or policies and positions of HTA agencies, and perhaps even if informal or formal discussions with HTA agencies in advance of the HTA, could have shaped whether the RWE was tabled, or whether it was and disregarded, but not reported in the final HTA reports.

Therefore, while HTA is at least theoretically acceptable to most HTA agencies, our analysis shows that it is not always used, or its use differs across agencies. We explore here some of the main barriers to its wider use. The order in which they are discussed does not imply their relative importance.

There is a lack of consistent terminology used for RWE

When RWE is used, the HTA agency reports did not apply a universal categorisation to describe the RWD sources used. For example, reference was made to 'natural history' but with little more to characterise the underlying RWD for Evrysdi in HTA reports from Canada, England, and France, and for Zolgensma in HTA reports from Australia, Canada, England, and France. In other cases, the source was more clearly identified, for example, with references to chart reviews in the HTAs of Luxturna in Canada and England.

It can, however, get very confusing. For example, the HTA of Zolgensma in Australia identified eight natural history studies. Two further studies identified in the Australian HTA—but which were not identified as natural history studies but instead as trials—were cited in the Canadian HTA as trials using "a natural history cohort" (STR1VE-US and the SPR1NT). These were described as clinical studies in the French HTA and as open-label single-arm phase 3 studies in England's HTA. There is just one common study in the Australia and the French HTA, the PNCR study.

Such varying terminology naturally leads to confusion. "The lack of agreement among assessors on what RWE is, is not an academic issue; it has serious real-world consequences for patients, so that some get access and others don't," said Durhane Wong-Rieger, President and CEO of the Canadian Organization for Rare Disorders.

There is a lack of early engagement and clear guidance

The views of HTA agencies on the value of the RWE that was considered vary. For example, the same RWE has been accepted by some agencies, but has not been reported in HTAs from other agencies. This implies that there is not only a difference of opinion on the added value of the RWE between companies who submit the RWE and the agencies who review it, but also differences of opinion between agencies.

What might explain some of these differences between HTAs? Interviewees stressed that the important focus was on ensuring that the RWE was fit for purpose; and that, of course, is where companies and HTA agencies may differ in their views. "Of course, what matters is that the source is fit for purpose, says Don Husereau, Adjunct professor, University of Ottawa, School of Epidemiology and Public Health. Professor Durand-Zaleski agrees, adding that, "I think it's true for every HTA agency, there is openness [to RWE], as long as the research question is clear, the quality of the data is good, that its use can be justified. And as long as it does answer a well-framed research question."

There are also sometimes limitations in the underlying RWD, and different agencies may have different degrees of tolerance about what to accept. "The problem at the moment is there are lots of ideas about how, in theory, we should be able to use RWD. But in reality, I think we're

still in a place where the granularity of that data isn't sufficient, especially if you're looking to go abroad and use other people's data then it's not readily comparable. It does need international collaboration" remarks Professor Leng. "What you need to do is agree on what the questions are and what data you should be collecting, so that it's there [when you need it for HTA]."

We did hear from one interviewee that HTA agencies are open to RWE, albeit that this was not necessarily explicit in the guidance for industry. "Canada has always been open to the receipt and use of RWE. Maybe it's not really explicit in their guidelines, they have simply asked manufacturers to submit relevant evidence", explained Mr Husereau. "They've not really suggested what the study designs had to be and there's nothing that has stopped manufacturers from actually submitting real-world studies if they had them."

Finally, particularly in the case of data collected across a range of sources, the challenge can be whether there is sufficient linkage to ensure the most valuable RWD is available. Professor Durand-Zaleski suggested that, "The hurdle is really logistics. So for registries, some of them are extremely well run, others not so well. In theory, you can link them to the national claims database, which would then make something very powerful, except it takes forever and requires dedicated resources."

There is a lack of evidence on the impact of RWE

Given the challenges in determining if, what type, and how RWE was used in HTA, it follows that it is also difficult to determine the impact of RWE on HTA decision-making.

The influence of RWE will reflect its underlying data source as well as the methods used to produce the evidence—these can be difficult to untangle, particularly as there will have been a variety of other factors driving the final HTA recommendations too. What is perhaps most striking is the consistently inconsistent role of RWE in HTA decision-making.

The same issue of a lack of evidence of impact applies more generally to RWE derived from patient experience. For example, evidence from patients and their representatives about their experience with a new treatment or their experience of a disease. Such evidence can provide a valuable understanding of the potential difference a new treatment could make. Whilst patients or patient groups may not know the difference their evidence has made, there is a belief that it will have been considered by the HTA agency. We heard from Mr Kent, "The patient group will not necessarily have that knowledge about the weight of their evidence in shaping the decision. That's not to say that it doesn't have a weight."

Looking to the future

At least in theory, HTA agencies welcome the use of RWE. Mr Husereau said, "HTA is open to looking at whatever provides added value. We want to look at the totality of the evidence, we're always interested. Particularly when we have trials that might have interim data."

However, our investigation of 'real-life decision-making' using RWE by HTA agencies, suggests that there remains a lack of certainty when it comes to the use of RWE. This was the case even for the eight highly innovative therapies we considered—those that are either ATMPs or have come through EMA's PRIME pathway. These are therapies where RWE is most likely to be needed, given the limitations of available trial data. RWE usage for less innovative new therapies is likely to be more limited still.

This is concerning. Not only in terms of whether all the relevant evidence is being used to inform HTA, but it also raises ethical concerns. We heard from a patient representative who suggested that patients would be surprised and disappointed that the data studiously collected on their experience was being disregarded by HTA agencies. Furthermore, some patients and patient groups may have only agreed to have their personal data collected because they were told it would help others in their position to gain access to the best therapy for them. It is therefore important that industry, HTA agencies, and other stakeholders work together to promote the fair assessment of RWE.

There are a number of limitations to our work. First, as noted, the therapies were particularly innovative in nature, and so the findings are not applicable to all therapies or therapy areas. Second, the HTA decisions reflect the situation before 2021. Third, our research was neither systematic nor comprehensive—the field of RWE and HTA is vast and this paper has necessarily been pragmatic. Similarly, there is more that future work could do. There is scope to dig more deeply to explore these issues raised in this report, for example, through reviewing all publicly available documents that cover the RWE submitted to HTAs (although this is not available for all HTA agencies). This would help shine more light on the underlying data sources, the methods used, and the reasons why RWE was used, or not, by the HTA agency. Research could also explore how RWE has played a role in re-assessments. Similarly a fuller picture of the influence of RWE on access would also mean widening the agencies looked at.

Nevertheless, clear themes have emerged from our investigation. It is apparent that while the use of RWE varies, it can and does add value when it has been used. However, the different terminology used by HTA agencies, differences in opinion on the merits of the available RWE, a lack of an evidence base, and an overarching lack of transparency continues to hinder its use.

In order for RWE to make a more significant impact in the assessment of new therapies, we suggest the following five takeaways.

HTA agencies should declare a greater openness to the use of RWE

Companies and HTA agencies—and other stakeholders—need to shift their mind-set to ensure that there is an openness to consider RWE on relative treatment effects within HTA. That does not mean that any RWE should be included, rather it must be fit for purpose.

Individuals in the world of HTA are keen for this to happen. Results of a survey of 22 HTA agencies published in 2022 have found that HTA agencies are open to using RWE. Yet the majority (82%) of respondents indicated a need to see wider systematic use of RWD—and the evidence that flows from it—in HTA.9 Action on the ground is happening. Work such as the RWE framework from NICE is seen as a way to encourage companies to bring forward RWE. Professor Leng says that, "The RWE framework [from NICE] gives companies an open door to say look, you can think about the RWD that can be useful. It's not setting everything out, but the door is open."

Suggested initial action: *That HTA agencies review their guidance documents for industry to explore how to make an openness to RWE more explicit*

HTA agencies and industry need to develop a shared terminology

Companies, HTA agencies and others also need to be mindful of their language and work together to agree meaningful terminology to use in HTA. All stakeholders should have a common understanding of RWE for relative treatment effects. If all stakeholders could talk the same talk it will help provide a common starting point for discussions on what RWE can add value.

Education on RWE was also put forward as a need by one interviewee. "I think there's a lot of education that needs to be done around the value proposition [of RWE], said a Professor, leading research on medicine use, based in Australia. "There's some really great stuff that's coming out of the US [on RWE]. There's stuff going on in the EU and NICE is doing great work. We don't need to reinvent the wheel. I think it's becoming a bit more global in the way that we think about this."

Suggested initial action: *That HTA agencies adopt and use a pre-existing glossary of terms, such as that provided by RWE navigator, part of the GetReal initiative, adapting these as necessary over time.*

Early engagement and collaboration between HTA agencies and industry on the potential use of RWE for relative treatment effects should be normalised

Using the same terminology will be a good start, but collaboration is also vital to develop a shared view on what RWE for relative treatment effects is acceptable and in what circumstances. And this is not a one-step fix. Collaboration will be particularly useful as RWE continues to evolve as all stakeholders will need to keep pace with changing methods.

An important part of collaboration is early engagement between companies and HTA agencies. In the HTA of Yescarta, for example, the

NICE Evidence Review Group highlighted how SCHOLAR-1 could have been validated with data from the Haematological Malignancy Research Network (HMRN) registry. Yet the reality was that this was not available within the timelines of the appraisal. Could earlier discussion have enabled such validation to take place?

"Everyone needs to start thinking about getting the information, and the evidence together earlier, so that you don't get to the HTA and they say, what can you tell us about this in particular?", explains Mr Kent, "Because then you turn around and say, well, if we'd known you were going to ask if we could have collected it, you know, but as we didn't, it would be disproportionately difficult to go back and collected now."

Dr Wong-Rieger agreed, adding "in order to have meaningful RWE, companies and HTA agencies need to collaborate proactively when designing clinical trials and, importantly, they must engage at the same time with the patient community."

Suggested initial action: *That HTA agencies and industry add RWE as a standing agenda item during early engagement discussions.*

HTAs should promote transparency in their use of RWE to support the development of an evidence base

Transparency is also needed so that stakeholders can see what RWE was used, in what way, and what difference it has made to decisions made by HTA agencies. To facilitate this, HTA agencies should make clear statements in their final HTA reports to identify if RWE was tabled for consideration, what type of RWE it was, and the underpinning type of RWD. Finally, HTA reports should make clear what impact it had, if any, on their recommendations.

An increase in transparency would also provide the basis for the development of an evidence base. As more RWE is used in HTA there is an opportunity for all stakeholders to take stock and learn from practical experience, creating more confidence about when—and when not—to use RWE for the assessment of relative treatment effects in HTA.

Collectively, this progress should provide a clearer signal to those producing RWE on treatment effectiveness on what is needed to support decision-making by HTA agencies. Thus providing a virtuous circle as experience with RWE on relative treatment effects in HTA builds over time.

Suggested initial action: *HTA agencies add a section in their final decision documents for a discussion of their use of—or disregarding of—RWE for the final assessment decision*

As RWE continues to evolve, expertise within agencies need to be maintained and promoted throughout the agency

Virtuous circles develop over time, and many of our interviewees spoke of how RWE—its collection and analysis—is continuing to develop. There is clear support in principle for increased use of RWE in HTA, and there is plainly extensive RWE expertise in agencies. This expertise will need to be maintained and built on as RWE continues to evolve—"RWE is changing" says Mr Husereau, "the methods are evolving all the time".

Furthermore, while many HTA agencies have technical teams with expertise in RWE, it is important that a good understanding of RWE is found throughout the organisation. Committees rely on input from technical experts, which is right and natural, but to understand expert input itself requires some degree of expertise in order to understand it and apply it in context.

Suggested initial action: *Technical teams in HTAs should have as part of their role the dissemination of RWE expertise throughout the agency as a whole*

Appendix 1: Methods

The research underpinning this report was based on three work-streams.

1. A desk-based environmental scan was undertaken to understand the contemporary landscape and identify ongoing initiatives on RWE in HTA. This was undertaken between January 2022 and May 2022, and so predates key publications such as the final RWE framework published by NICE on 23 June 2022.

2. A review of the first HTA reports from Australia (Pharmaceutical Benefits Advisory Committee (PBAC), the Medical Services Advisory Committee (MSAC)), Canada (Canadian Agency for Drugs and Technologies in Health (CADTH)), France (Haute Autorité de santé (HAS)), England (National Institute for Health and Care Excellence (NICE)), and Germany (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG)) for five Advanced Therapy Medicinal Products (ATMPs), Novartis' Kymriah, Novartis' Luxturna, Kite's Tecartus, Kite's Yescarta, Novartis' Zolgensma. ATMPs are medicines based on genes, tissues or cells and are considered to be groundbreaking.[25] Three treatments that had gone through the PRIME programme at EMA, a programme that seeks to speed up regulatory evaluation,[26] were also reviewed (Roche's Evrysdi, Genentech's Polivy, and Roche's Rozlytrek). This review identified dates of the regulatory and HTA activities, regulatory procedures, as well as the use of RWE for relative treatment effects in HTA.

3. One-to-one interviews were undertaken with six experts. No experts from Germany took up the invitation to participate.

The initial focus was on Advanced Therapy Medicinal Products (ATMPs), a classification used by the European Medicines Agency (EMA) but not used in all jurisdictions. ATMPs are medicines based on genes, tissues or cells and are considered to be groundbreaking.[25] Only 21 ATMPs have been approved by the EMA between 2016 and April 2022, and five of these have been withdrawn.[28] Approved ATMPs are typically for very rare conditions and have often had small trials with only limited data available on long-term effectiveness.[29]

RWE may be more likely to be drawn upon for ATMPs given their recognized data challenges for decision-making.[9] Five ATMPs - Novartis' Kymriah, Novartis' Luxturna, Kite's Tecartus, Kite's Yescarta, Novartis' Zolgensma—had been given marketing authorisation in each jurisdiction and had final first HTA reports publicly available from at least four of the five countries in scope.

A further three examples—Roche's Evrysdi, Genentech's Polivy, and Roche's Rozlytrek – were identified as examples from EMA's PRIME programme. PRIME is targeted at treatments for unmet medical need and aim to speed up regulatory evaluation.[26]

Objective data were abstracted for each of the eight treatments from the regulatory agency (i.e. type and date of marketing authorisation (ma)). Objective data was abstracted from the

final main report from the first HTA (i.e. date of HTA, the use of RWE) and the reports were also used to draw out subjective data (i.e. the impact of the RWE on HTA recommendation). This means that the full details of the RWE and how it was used may not have been identified where it is presented in other public documents. The impact of RWE is not clearly stated by HTA agencies which means that other researchers may have come to a different determination. Relying on the main HTA reports made the research more feasible (some agencies can provide 100s of pages for an individual HTA) and will also likely be the focus of many stakeholders when understanding on what basis an HTA decision is made.

This approach means that if the first HTA has been subsequently updated this is not captured in our analysis. Similarly, there may be information available on the RWE—either at the time of the first HTA or after it—that has not been captured or otherwise does not appear in the HTA report. As a final note, given the scale of the literature that cites RWE we did not undertake a comprehensive systematic review of that evidence base.

Appendix 2: Evidence tables

TABLE A1: Roche, Evrysdi (Risdiplam), Spinal Muscular Atrophy (SMA) with clinical trial evidence available from RCTs vs placebo, a single-arm trial and other open-label trials

	Australia	Canada	England	France	Germany
REGULATORY DECISION					
Regulatory details	Orphan Priority Full	 Priority Full	Orphan Accelerated PRIME Full	Orphan Accelerated PRIME Full	Orphan Accelerated PRIME Full
Date of ma	02/06/2021	14/04/2021	26/03/2021	26/03/2021	26/03/2021
HTA DECISION					
HTA agency	PBAC	CADTH	NICE	HAS	IQWiG
Date of final first HTA	05/07/2021(p)	27/08/2021	16/12/2021	25/10/2021	29/07/2021
Final first HTA recommendation	Restricted* & conditional	Conditional	Conditional	Positive	Restricted**
USE OF REAL-WORLD EVIDENCE					
Use of RWE in first HTA	Not found	Yes	Yes	Yes	Not found
What RWE used for in first HTA	-	Comparator	Comparator	Comparator	-
Type of RWE	-	Natural history	Natural history, Chart review	Natural history	-
Impact of RWE on final first HTA recommendation	-	**Positive**	**Positive**	**Neutral/ uncertain**	
HTA recommendation for future use of RWE	Australian patient registry	Not found	Managed access agreement	French patient registry	Not found

Notes:
ma = marketing authorization
(p) = denotes parallel process for approval from TGA and PBAC.
– = not applicable
* Patients with SMA Types 1, 2 or 3a who are aged 18 years or under at treatment initiation
** Patients with SMA Ttype 1
Canada has no orphan designation.

TABLE A2: Novartis, Kymriah (Tisagenlecleucel), Diffuse large B-cell lymphoma (DLBCL) with clinical trial evidence available from single-arm trials

	Australia	Canada	England	France	Germany
REGULATORY DECISION					
Regulatory details	Full	Full	ATMP Orphan Accelerated PRIME Full	ATMP Orphan Accelerated PRIME Full	ATMP Orphan Accelerated PRIME Full
Date of ma	19/12/2018	05/09/2018	22/08/2018	22/08/2018	22/08/2018
HTA DECISION					
HTA agency	MSAC	CADTH	NICE	HAS	IQWiG
Date of final first HTA	09/04/2019	15/01/2019	13/03/2019	12/12/2018	14/09/28
Final first HTA recommendation	Conditional	Conditional	Conditional (Cancer Drugs Fund)	Positive	-
USE OF REAL-WORLD EVIDENCE					
Use of RWE in first HTA	Not found	Not found	Yes	Yes	*
What RWE used for in first HTA	-	-	Treatment effect	Comparator	-
Type of RWE	-	-	Small observational study Retrospective observational studies Database	Retrospective study Observational studies	-
Impact of RWE on final first HTA recommendation	-	-	**Neutral/ uncertain**	**Disregarded**	-
HTA recommendation for future use of RWE	Not found	Canadian patient registry	Systemic Anti-Cancer Therapy Database	French patient registry	-

Notes:
ma = marketing authorization
– = not applicable
* IQWIG conducted a budget impact assessment to determine if an added benefit evaluation was required given an orphan designation
Canada has no orphan designation.

TABLE A3: Novartis, Luxturna (Voretigene neparvovec), Vision loss due to inherited retinal dystrophies caused by RPE65 gene mutations with clinical trial evidence available from an RCT vs best supportive care

	Australia	Canada	England	France	Germany
REGULATORY DECISION					
Regulatory details			ATMP	ATMP	ATMP
	Orphan		Orphan	Orphan	Orphan
	Full	Full	Full	Full	Full
Date of ma	05/08/2020	13/10/2020	22/11/2018	22/11/2018	22/11/2018
HTA DECISION					
HTA agency	MSAC	CADTH	NICE	HAS	IQWiG
Date of final first HTA	27/11/2020*	12/11/2020	03/04/2019	03/04/2019	03/04/2019
Final first HTA recommendation	Conditional	Conditional	Conditional	Positive	*
USE OF REAL-WORLD EVIDENCE					
Use of RWE in first HTA	Not found	Yes	Yes	Yes	-
What RWE used for in first HTA	-	Comparator	Treatment effect	Treatment effect	-
Type of RWE	-	Chart review	Chart review, 'longitudinal study'	ATU (case report for 1 pt)	-
Impact of RWE on final first HTA recommendation	-	**Disregarded**	**Neutral/ uncertain**	**Neutral/ uncertain**	-
HTA recommendation for future use of RWE	Novartis international registry	Not found	Not found	French patient registry	-

Notes:
ma = marketing authorization
– = not applicable
ATU = temporary authorization for use programme
* IQWIG conducted a budget impact assessment to determine if an added benefit evaluation was required given an orphan designation
Canada has no orphan designation.

TABLE A4: Genentech, Polivy (Polatuzumab vedotin), Diffuse Large B-cell Lymphoma (DLBCL) ineligible for stem cell transplantation with clinical trial evidence available from an open-label RCT

	Australia	Canada	England	France	Germany
REGULATORY DECISION					
Regulatory details	Full	Full	Orphan PRIME Conditional	Orphan PRIME Conditional	Orphan PRIME Conditional
Date of ma	18/10/2019	09/07/2020	16/01/2020	16/01/2020	16/01/2020
HTA DECISION					
HTA agency	PBAC	CADTH	NICE	HAS	IQWiG
Date of final first HTA	01/11/2019 (p)	21/04/2021	23/09/2020	10/06/2020	15/05/2020
Final first HTA recommendation	Negative	Conditional	Conditional	Negative	*
USE OF REAL-WORLD EVIDENCE					
Use of RWE in first HTA	Not found	Yes	Not found	ATU is in place, but no pts treated	-
What RWE used for in first HTA	-	Comparator	-	-	-
Type of RWE	-	Database	-	-	-
Impact of RWE on final first HTA recommendation	-	**Neutral/ uncertain**	-	-	-
HTA recommendation for future use of RWE	Not found	Not found	Not found	Not found	-

Notes:
ma = marketing authorization
(p) = denotes parallel process for approval from TGA and PBAC.
* IQWIG conducted a budget impact assessment to determine if an added benefit evaluation was required given an orphan designation
– = not applicable
Canada has no orphan designation.

TABLE A5: Roche, Rozlytrek (Entrectinib), ROS1-positive Non-Small Cell Lung Cancer (NSCLC) with clinical trial evidence available from single-arm trials

	Australia	Canada	England	France	Germany
REGULATORY DECISION					
Regulatory details	Provisional	Conditional	PRIME Conditional	PRIME Conditional	PRIME Conditional
Date of ma	14/05/2020	10/02/2020	31/07/2020	31/07/2020	31/07/2020
HTA DECISION					
HTA agency	PBAC	CADTH	NICE	HAS	IQWiG
Date of final first HTA	01/03/2020 (p)	27/01/2021	12/08/2020	21/07/2021	01/12/2020
Final first HTA recommendation	Positive	Conditional	Conditional	Negative	Negative
USE OF REAL-WORLD EVIDENCE					
Use of RWE in first HTA	Not found	Not found	Not found	Not found	Yes
What RWE used for in first HTA	-	-	-	-	Comparator
Type of RWE	-	-	-	-	Healthcare database (Flatiron Health)
Impact of RWE on final first HTA recommendation	-	-	-	-	**Disregarded**
HTA recommendation for future use of RWE	Not found	Not found	Not found	Yes (not stated)	Not found

Notes:
ma = marketing authorization
(p) = denotes parallel process for approval from TGA and PBAC.
– = not applicable
Canada has no orphan designation.

TABLE A6: Kite Pharma, Tecartus (Brexucabtagene autoleucel), Mantel Cell Lymphoma (MCL) with clinical trial evidence available from a single-arm trial

	Australia	Canada	England	France	Germany
REGULATORY DECISION					
Regulatory details			ATMP	ATMP	ATMP
			Orphan	Orphan	Orphan
		Priority	PRIME	PRIME	PRIME
	Full	Full	Conditional	Conditional	Conditional
Date of ma	16/07/2021	08/06/2021	14/12/2020	14/12/2020	14/12/2020
HTA DECISION					
HTA agency	MSAC	CADTH	NICE	HAS	IQWiG
Date of final first HTA	30/07/2021	24/08/2021	24/02/2021	21/04/2021	12/05/2021
Final first HTA recommendation	Positive	Conditional	Conditional (Cancer Drugs Fund)	Positive	*
USE OF REAL-WORLD EVIDENCE					
Use of RWE in first HTA	Yes	Yes	Yes	Yes	-
What RWE used for in first HTA	Comparator	Comparator	Comparator	Comparator	-
Type of RWE	Chart review, Retrospective observational studies	Retrospective studies	Cohort study	Real-life study	-
Impact of RWE on final first HTA recommendation	**Neutral/ uncertain**	**Disregarded**	**Neutral/ uncertain**	**Disregarded**	-
HTA recommendation for future use of RWE			Systemic Anti-Cancer Therapy Database		-

Notes:
ma = marketing authorization
* IQWIG conducted a budget impact assessment to determine if an added benefit evaluation was required given an orphan designation
– = not applicable
Canada has no orphan designation.

TABLE A7: Kite Pharma, Yescarta (Axicabtagene ciloleucel), B-cell Lymphoma with clinical trial evidence available from an open-label single-arm trial

	Australia	Canada	England	France	Germany
REGULATORY DECISION					
Regulatory details	Full	Full	ATMP Orphan PRIME Full	ATMP Orphan PRIME Full	ATMP Orphan PRIME Full
Date of ma	11/02/2020	13/02/2019	23/08/2028	23/08/2028	23/08/2028
HTA DECISION					
HTA agency	MSAC	CADTH	NICE	HAS	IQWiG
Date of final first HTA	16/01/2020	20/08/2019	07/12/2019	*	29/01/2019
Final first HTA recommendation	Conditional	Conditional	Conditional (Cancer Drugs Fund)	-	-
USE OF REAL-WORLD EVIDENCE					
Use of RWE in first HTA	Yes	Yes	Yes	-	**
What RWE used for in first HTA	Comparator	Treatment effect	Comparator	-	-
Type of RWE	Retrospective study	Real-world setting	Healthcare databases	-	-
Impact of RWE on final first HTA recommendation	**Neutral/ uncertain**	**Neutral/ uncertain**	**Neutral/ uncertain**	-	-
HTA recommendation for future use of RWE	Australian patient registry	Canadian patient registry	Systemic Anti-Cancer Therapy Database	-	-

Notes:
ma = marketing authorization
* First HTA not found in the public domain
** IQWIG conducted a budget impact assessment to determine if an added benefit evaluation was required given an orphan designation
– = not applicable
Canada has no orphan designation.

TABLE A8: Novartis, Zolgensma (Onasemnogene abeparvovec), Spinal Muscular Atrophy (SMA) with biallelic mutations in the survival motor neuron 1 (SMN1) gene with one to three copies of the SMN2 gene with clinical trial evidence available from single-arm trials

	Australia	Canada	England	France	Germany
REGULATORY DECISION					
Regulatory details	Full	Priority Full	ATMP Orphan PRIME Conditional	ATMP Orphan PRIME Conditional	ATMP Orphan PRIME Conditional
Date of ma	24/02/2021	15/12/2020	18/05/2020	18/05/2020	18/05/2020
HTA DECISION					
HTA agency	PBAC	CADTH	NICE	HAS	IQWiG
Date of final first HTA	24/09/2021(p)	26/03/2021	07/07/2021	16/12/2020	12/08/2021
Final first HTA recommendation	Conditional	Conditional	Conditional	Restricted	Negative
USE OF REAL-WORLD EVIDENCE					
Use of RWE in first HTA	Yes	Yes	Yes	Yes	Not found
What RWE used for in first HTA	Comparator	Comparator	Comparator	Comparator	-
Type of RWE	EAPs (Australia and international), Natural history study, Observational study	Natural history studies	Natural history studies	Natural history studies, Chart review	-
Impact of RWE on final first HTA recommendation	**Positive**	**Positive**	**Positive**	**Positive**	-
HTA recommendation for future use of RWE	Australian patient registry	Not found	Not found	French patient registry, ATU	Not found

Notes:
ma = marketing authorization
(p) = denotes parallel process for approval from TGA and PBAC.
– = not applicable
ATU = temporary authorization for use programme
EAP = Early Access Programme
Canada has no orphan designation.

References

1 Makady A, de Boer A, Hillege H, et al. What Is Real-World Data? A Review of Definitions Based on Literature and Stakeholder Interviews. Value in Health. 2017;20(7):858-65.

2 Patel D, Grimson F, Mihaylova E, et al. Use of External Comparators for Health Technology Assessment Submissions Based on Single-Arm Trials. Value in Health. 2021;24(8):1118-25.

3 McDonald L. Florence Nightingale and the early origins of evidence-based nursing. Evidence Based Nursing. 2001;4(3):68.

4 ISPOR. Real-World Evidence. Lawrenceville, NJ USA: The Professional Society for Health Economics and Outcomes Research. Available from: https://www.ispor.org/strategic-initiatives/real-world-evidence.

5 Blonde L, Khunti K, Harris SB, et al. Interpretation and Impact of Real-World Clinical Data for the Practicing Clinician. Advances in therapy. 2018;35(11):1763-74.

6 O'Rourke B, Oortwijn W, Schuller T. The new definition of Health Technology Assessment: A milestone in international collaboration. International Journal of Technology Assessment in Health Care. 2020;36(3):187-90.

7 European Commission. Study on the use of Real-World Data (RWD) for research, clinical care, regulatory decision-making, Health Technology Assessment, and policy-making : final report and recommendations. Luxembourg: Publications Office of the European Union; 2021.

8 NICE. Real-World Evidence Framework Update. London, United Kingdom: National Institute for Health and Care Excellence, 2022.

9 Hogervorst MA, Pontén J, Vreman RA, et al. Real World Data in Health Technology Assessment of Complex Health Technologies. Frontiers in Pharmacology. 2022;13.

10 Agrawal S, Arora S, Vallejo JJ, et al. Use of single-arm trials to support malignant hematology and oncology drug and biologic approvals: A 20-year FDA experience. Journal of Clinical Oncology. 2021;39(15_suppl):e13572-e.

11 Jaksa A, Wu J, Jónsson P, et al. Organized structure of Real-World Evidence best practices: moving from fragmented recommendations to comprehensive guidance. Journal of Comparative Effectiveness Research. 2021;10(9):711-31.

12 Makady A, Ham Rt, de Boer A, et al. Policies for Use of Real-World Data in Health Technology Assessment (HTA): A Comparative Study of Six HTA Agencies. Value in Health. 2017;20(4):520-32.

13 GetReal. GetReal Institute. Heidelberglaan, Netherlands: GetReal Institute. Available from: https://www.getreal-institute.org/.

14 WHO. Emerging trends and technologies: a horizon scan for global public health. Geneva, Switzerland: World Health Organization 2022. Available from: https://www.who.int/publications/i/item/9789240044173.

15 RWE4Decisions. Real-World Data Sources and Quality Round Table Brussels, Belgium: RWE4Decisions Available from: https://mcusercontent.com/29c7f99b2e27d60bf06427cc1/files/10239b1a-9f52-bfec-1339-d6c74c16022d/220301_DRAFT_Agenda_RWD_Sources_and_Quality_23_March.pdf.

16 RWE4Decisions. Public Webinar Series Supporting HTA/Payer decisions making: National health data initiatives in Finland, Spain and France. Brussels, Belgium RWE4Decisions. Available from: https://rwe4decisions.com/event/public-webinar-series-national-health-data-initiatives-in-finland-spain-and-france/.

17 NICE. Real-World Evidence framework feedback. National Institute for Health Care Excellence; [2022-03-30]. Available from: https://www.nice.org.uk/about/what-we-do/real-world-evidence-framework-feedback.

18 NICE. NICE strategy 2021 to 2026. London, United Kingdom: National Institute for Healthcare and Excellence. Available from: https://static.nice.org.uk/NICE%20strategy%202021%20to%202026%20-%20Dynamic,%20Collaborative,%20Excellent.pdf.

19 Eversana. IQWiG Tasked by G-BA to Collect Application-Related Data on CAR-T Therapies Chicago, Illinois, United States: Eversanacompany; [2021-04-02]. Available from: https://www.eversana.com/2021/04/02/iqwig-tasked-by-g-ba-to-collect-application-related-data-on-car-t-therapies/.

20 Haute Autorité De Santé. Real-world studies for the assessment of medicinal products and medical devices. Paris, France: Haute Autorité De Santé, 2021. Available from: https://www.has-sante.fr/upload/docs/application/pdf/2021-06/real-world_studies_for_the_assessment_of_medicinal_products_and_medical_devices.pdf.

21 Haute Autorité De Santé. Real-life studies - Listing of data sources that can be used to respond to respond to HAS requests. Paris, France: Haute Autorité De Santé. Available from: https://www.has-sante.fr/jcms/p_3333630/fr/etudes-en-vie-reelle-recensement-des-sources-de-donnees-mobilisables-pour-repondre-aux-demandes-de-la-has.

22 CADTH. CADTH Expands Scientific Advice Program to Include Advice on Real-World Evidence Ottawa, Canada: Canada's Drug and Health Technology Agency. Available from: https://www.cadth.ca/news/cadth-expands-scientific-advice-program-include-advice-real-world-evidence.

23 CADTH. Real-World Evidence for Decision-Making. Ottawa, Canada: Canada's Drug and Health Technology Agency. Available from: https://www.cadth.ca/real-world-evidence-decision-making.

24 Fontrier A-M, Visintin E, Kanavos P. Similarities and Differences in Health Technology Assessment Systems and Implications for Coverage Decisions: Evidence from 32 Countries. PharmacoEconomics - open. 2022;6(3):315-28.

25 EMA. Advanced therapy medicinal products: Overview Amsterdam, The Netherlands: European Medicines Agency Available from: https://www.ema.europa.eu/en/human-regulatory/overview/advanced-therapy-medicinal-products-overview.

26 EMA. PRIME: priority medicines. Amsterdam, The Netherlands: European Medicines Agency [07/05/2018]. Available from: https://www.ema.europa.eu/en/human-regulatory/research-development/prime-priority-medicines.

27 NICE, NHS. Response to engagement on proposals for the Innovative Medicines Fund. London, United Kingdom: NHS England and NHS Improvement 2022. Available from: https://www.england.nhs.uk/wp-content/uploads/2022/06/B1685-response-to-public-engagement-on-proposals-for-the-innovate-medicines-fund-june-2022.pdf.

28 EMA. European Medicines Agency Amsterdam, The Netherlands: European Medicines Agency Available from: https://www.ema.europa.eu/en.

29 ReMap consulting. Why is the number of advanced therapy medicinal product (ATMP) withdrawals from the European market rising? Switzerland: Remapconsulting; [2022-02-07]. Available from: https://remapconsulting.com/atmps-in-europe/.

ECONOMIST IMPACT

LONDON

20 Cabot Square
London, E14 4QW
United Kingdom
Tel: (44.20) 7576 8000
Fax: (44.20) 7576 8500
Email: london@economist.com

GENEVA

Rue de l'Athénée 32
1206 Geneva
Switzerland
Tel: (41) 22 566 2470
Fax: (41) 22 346 93 47
Email: geneva@economist.com

NEW YORK

750 Third Avenue
5th Floor
New York, NY 10017
United States
Tel: (1.212) 554 0600
Fax: (1.212) 586 1181/2
Email: americas@economist.com

DUBAI

Office 1301a
Aurora Tower
Dubai Media City
Dubai
Tel: (971) 4 433 4202
Fax: (971) 4 438 0224
Email: dubai@economist.com

HONG KONG

1301
12 Taikoo Wan Road
Taikoo Shing
Hong Kong
Tel: (852) 2585 3888
Fax: (852) 2802 7638
Email: asia@economist.com

SINGAPORE

8 Cross Street
#23-01 Manulife Tower
Singapore
048424
Tel: (65) 6534 5177
Fax: (65) 6534 5077
Email: asia@economist.com