A Review of Real-World Evidence in HTA Decision-Making of Gene Therapies in the US, Canada, UK, EU4, and Japan

HTA34

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Introduction

- Evidence submitted for health technology assessments (HTA) of gene therapies (GT) may be limited and associated with uncertainty. Real-world evidence (RWE) may address these uncertainties, as it may be able to demonstrate a GT long-term benefit and bridge evidence gaps in regulatory and HTA submissions.
- For this reason, many HTA bodies have adopted guidelines and are increasingly requesting post-launch RWE collection for appraisals. However, the approach to use RWE and the requirements for this type of evidence vary between HTAs.
- With 381 ongoing trials (57 Phase III), the GT landscape is growing, with many GTs expected to see market access within a short period between one another[1]; thus, understanding the role for RWE in HTA and its inclusion in GT evidence packages is critical for GT developers.

Objective

- To evaluate the role of RWE in the HTA decision-making of GTs.
- To understand the prevalence of RWE in previous HTA reports.
- To understand the context in which RWE have been used in HTAs for GTs.

Methods

- Official regulatory websites in the US, Canada, UK, EU4 (France, Germany, Italy, and Spain), and Japan were reviewed to identify GTs with current marketing authorization (MA).
- Official HTA websites of the countries in scope were reviewed to extract HTA reports of these GTs where publicly available.
  - These HTA bodies include ICER, CADTH, NICE, G-BA, HAS, AIFA, and HAS.
  - In the case of Japan, the PMDA was used. Prior to 2019, when the cost-effectiveness assessment (CEA) scheme was adopted, Japan did not have a formal HTA body; thus, the official PMDA site was used, noting that it is the main Japanese regulatory body.
- From these HTAs reports, data relevant to RWE were then further extracted and analyzed.
  - Data fields extracted for analysis included, among other domains, date assessed, indication, type of RWE, and context of RWE request.

Results

- A total of 18 GTs were found to have MA within the geographical scope, out of which, 17 GTs had HTAs and 1 was approved but not yet assessed.
- A total of 61 HTA reports and an additional 6 Japanese reports were extracted.
  - These included initial assessments, re-assessments, and assessments of all indications where there were multiple indications for a single therapy (e.g., Yescarta®).
- Out of a total of 57 HTA reports, 48 reports (84%) mentioned RWE.
  - Out of these, 16 (33%) reports included RWE as part of submission, and 32 (67%) reports included an HTA request for RWE for various reasons (e.g., long-term follow-up).

Results (Cont'd)

- 100% of the GTs assessed by G-BA, AIFA and PMDA had RWE either presented alongside pivotal studies or RWE requested for follow-up.
- ICER noted a long-term RWE need for 70% of the GTs assessed, while 40% of GTs presented RWE in their evidence packages.
- AIFA has requested RWE as a condition for market authorization and every GT assessed included RWE in their evidence package.
- While none of the GTs assessed by AEMPS mentioned RWE as part of the reviewed evidence, ~67% of AEMPS reports mentioned RWE as a necessity to establish safety/efficacy of the GT.
- Most HTA bodies mentioned uncertainty of evidence submissions translating to real-world practice.

Table 1. RWE in HTA Decision-Making and RWE Role

Gene Therapy*	RWE in HTA Decision-Making for GTs							
	NICE (UK)	HAS (France)	GBA (Germany)	AIFA (Italy)	AEMPS (Spain)	ICER (US)	CADTH (Canada)	PMDA (Japan)
Hemgenix® (2022)	○	○	○	○	○	●	○	○
Adstiladrin® (2022)	○	○	○	○	○	●	○	○
Roctavian® (2022)	○	○	◐	○	○	●	○	○
Carvykti® (2022)	○	●	○	○	○	◐	○	○
Skysona® (2022)	○	○	○	○	○	○	○	○
Abecma® (2021)	○	●	◐	○	○	◐	◐	○
Breyanzi® (2021)	○	○	○	○	○	○	◐	●
Delytact® (2021)	○	○	○	○	○	○	○	●
Libmeldy® (2020)	●	●	●	●	○	○	○	○
Tecartus® (2020)	●	●	◐	◐	●	○	○	○
Zynteglo®** (2022)	○	○	○	○	○	●	○	○

● RWE requested by HTA body; ◐ RWE submitted in evidence package; ● RWE not mentioned in report; ● GT assessed; no official report available; ○ GT not appraised by HTA body

*GTs are listed by the year of their initial HTA and/or marketing authorization approval; study includes all HTAs and re-assessments to date of this poster;**Zynteglo obtained EMA approval in 2019, but has since withdrawn from the EU market, it was approved by the FDA in 2022

Table 1. RWE in HTA Decision-Making and RWE Role (Cont'd)

Gene Therapy	RWE in HTA Decision-Making for GTs							
	NICE (UK)	HAS (France)	GBA (Germany)	AIFA (Italy)	AEMPS (Spain)	ICER (US)	CADTH (Canada)	PMDA (Japan)
Zolgensma® (2019)	●	●	●	◐	●	●	◐	●
Collategene® (2019)	○	○	○	○	○	○	○	●
Luxturna® (2017)	●	●	◐	●	●	●	●	○
Yescarta® (2017)	◐	●	●	●	●	●	●	●
Kymriah® (2017)	◐	○	◐	◐	●	●	○	●
Strimvelis® (2016)	●	○	○	◐	○	○	○	○
Imlygic® (2015)	●	○	○	○	●	○	○	○

Abbreviations: RWE: Real-World Evidence; UK: United Kingdom; US: United States
List of full references and all abbreviations are available upon request.

Discussions

Inherent challenges are apparent in GTs' limited evidence packages

- GTs often target rare, severe diseases with small patient populations for which there are no current treatments or only symptomatic treatments are available. GTs are also often associated with high prices.
- Due to these characteristics, several major challenges are associated with their clinical trial designs, as they are often single-arm or open-label, with small sample sizes. Further, the duration of effect and safety in the long-term is often difficult to establish. Considering this and their high prices, there is often uncertainty around benefits.3,4
- However, due to their transformative nature, these therapies are increasingly approved based upon these limited evidence packages, despite being met with varying degrees of HTA and payer uncertainty.

RWE is being requested to address uncertainties around long-term benefit

- There are many types of RWE, including observational studies, registry data, prospective cohort studies, medical chart reviews, claims databases, etc. Collection of RWE has been used to mitigate uncertainties with short-term evidence, compare multiple alternative therapies, and examine outcomes in a diverse population reflective of clinical practice, amongst other ways to overcome GT assessment challenges.[3,5]
- In 32 (67%) of the reports, every HTA body requested RWE to address long-term follow-up of safety or efficacy of GTs, except for one report by ICER for Adstiladrin®. This report used RWE for a comparative effectiveness analysis and recommended developers conduct RWE for similar drugs for comparative data, especially patient-relevant outcomes.

Discussions (Cont'd)

- As noted, Japan had no formal HTA prior to 2019, yet 100% of the Japanese reports from PMDA requested RWE generation specific to the Japanese population to demonstrate and confirm efficacy and/or safety.
- CADTH in Canada systematically searches for and implements RWE in their assessments. In 3 out of 4 CADTH reports identified in this study, RWE was used as a source for comparator data for standard of care comparison or to inform the natural history of the disease. Canada and the US have both used RWE as model inputs for assessing GTs.
- Japan and Italy have already used RWE generated to re-assess products, specifically Yescarta® and Kymriah®. In Japan, this resulted in price reductions of both therapies.
  - Originally approved in Japan at JPY 33,493,407, Kymriah®'s price was reduced by 4.3% as a direct outcome of the CEA and re-assessment of the GT.
- All HTA bodies of in-scope countries have provided developers guidance reports on how to appropriately supplement their trial data with RWE.[6-11]

RWE as a critical part of Coverage with Evidence Development Agreements

- Several GTs have been reimbursed via coverage with evidence development (CED) agreements, which require RWE and additional evidence generation for payers to reimburse the therapies, to address payer concerns and uncertainties related to long-term outcomes and high prices.
- Reimbursement via CEDs is conditional and subject to change based on the RWE; France, UK, Italy, Germany and Spain have recommended and reimbursed GTs based on CEDs.

Conclusions

- RWE use has certainly increased in recent years and multiple HTA bodies have published guidance and frameworks for use of RWE in their submissions. An important point to highlight from this study is that multiple HTA bodies across Europe have used RWE to address uncertainties in the evidence package for novel GTs (considering the inherent challenges to conduct traditional randomized controlled studies for these health technologies) and other HTAs worldwide have even used RWE to re-assess products resulting in direct price reductions. Developers should plan for RWE collection in their clinical development programs and beyond to address such uncertainties and meet these national HTA requirements and prepare for price adjustments with a mitigation plan.
- However, the new guidance published as part of the new EU HTA Regulation, while it could support in harmonizing the approach to RWE collection, does not provide clarity on the cases for use of RWE and utilizes negative language when referring to non-randomized evidence. This should be carefully monitored by both manufacturers and national HTA bodies to ensure this important source of evidence continues to be leveraged to collect relevant outcomes and support timely patient access.

1. ARM Clinical Trials 2023
2. ICER Gene Therapy White Paper 2017
3. Overbeeke et al. MA challenges 2021
4. Carvalho et al. Regulator challenges 2019
5. Garrison et al. RWE use 2007
6. ISPOR Report Evidence Guidance 2020
7. NICE RWE Framework Guidance 2022
8. HAS RWE studies 2021
9. ICER RWE Framework White Paper 2021
10. CADTH RWE and RWD Guidance
11. PMDA Procedures for PM Study Plan 2018

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