Update of Our Review of Real-world Evidence in HTA Decision-making of Gene Therapies in the US, Canada, UK, EU4, and Japan

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Background

- Evidence submitted for health technology assessments (HTA) of gene therapies (GT) may be limited and associated with uncertainty. During our first review in 2023, we found that HTA bodies consistently request and use real-world evidence (RWE) to address these uncertainties, as it may be able to demonstrate long-term benefit and bridge evidence gaps in regulatory and HTA submissions. Furthermore, we found that HTA bodies worldwide have even used RWE to reassess products, where those reassessments resulted in direct price reductions.
- We are providing an update to our 2023 review by including reassessments of GTs we previously included, along with HTA reports of newly approved GTs. With this update, we aim to provide a better understanding of the role of RWE in HTA and its inclusion in GT evidence packages.

Objectives

- To update our prior research on the role of RWE in HTA decision-making for GTs in the US, Canada, UK, EU4, and Japan.
- To understand if any new GTs have been assessed using RWE and if any previous GTs assessed have been reassessed using RWE.

Methods

- Official regulatory websites in the US[1], Canada[2], UK, EU4 (France, Germany, Italy, and Spain), and Japan[3] 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.
  - HTA bodies include the National Institute for Health and Care Excellence (NICE)[4], Haute Autorité de santé (HAS)[5], Federal Joint Committee (G-BA)[6], Italian Medicines Agency (AIFA)[7], Spanish Agency of Medicines and Medical Devices (AEMPS)[8], Institute for Clinical and Economic Review (ICER)[9], and Canadian Agency for Drugs and Technologies in Health (CADTH)[10].
  - In the case of Japan, the Pharmaceutical and Medical Devices Agency (PMDA)[11] 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[11] site was used, noting that it is the main Japanese regulatory body.
- HTA reports from April 2023 to April 2024 were considered, as previous reports were included in our previous analysis. From these HTA reports, data relevant to RWE were further extracted and analyzed.
  - Data fields extracted for analysis included, among other domains, date assessed, type of RWE, context of RWE request, and HTA outcome.

Results

- Twenty-two GTs were found to have MA within the geographical scope, of which 13 GTs had HTAs and nine were approved but not yet assessed.
- Forty-one HTA reports were extracted.
  - These included latest assessments for drugs where there were multiple indications for a single therapy (e.g., Yescarta® and Kymriah®).
- Out of the 41 HTA reports, 34 (83%) mentioned RWE.
  - Of these, 21 (51%) reports included RWE as part of submission and eight (20%) included an HTA request for RWE for various reasons (e.g., long-term follow-up), five (12%) simply mentioned RWE without specific request or submission, and one (2%) mentioned an ongoing RWE study by the manufacturer.
- Since our April 2023 review, ICER[9] made three appraisals for new GTs about to launch, and no reassessments were found. Overall, it has reviewed 13 GTs of the 21 available in the US. This is explained by ICER's[9] methods. The US organization has been known to select drugs for review based on their potential to disrupt disease areas and anticipated budget impact and may not consistently review all drugs, unlike its European counterparts. Furthermore, ICER[9] has not often reassessed drugs and is more likely to update previous reports when substantial and significant new evidence is published. ICER[9] reports include recommendations to different stakeholders, and manufacturers are encouraged to develop cohort studies and RWE programs to evaluate longer-term safety and durability of GTs.
- In the UK, three new appraisals for GTs have been found. RWE was used to confirm efficacy, as inputs to cost-effectiveness models, or mentioned to highlight its inherent limitations and challenges. Interestingly, NICE[4] reported that for three GTs, it was not able to conduct an HTA due to the manufacturer not submitting their evidence package.

Results (cont.)

- In France, HAS[5] released 17 new reports since April 2023, which accounts for 41% of the reports in our study. Among those, six assessments were in new indications; six were renewals of early access; three were reassessments; and two were new early access requests. A HAS[5] review is mandatory for all drugs upon launch in France, which explains the high number of new indications. Additionally, as early access is granted for a year, renewals are triggered automatically on a yearly basis. Finally, reassessments of GTs in France are frequent, as those therapies are more likely to be conditionally approved with less mature data. HAS[5] usually requests confirmatory evidence with a deadline in the next few years, which triggers a reassessment procedure. Overall, HAS[5] consistently expressed interest in RWE on eligible and treated patients' characteristics; treatment history; disease characteristics at eligibility and re-injection; conditions of use; treatment strategy before and after re-injection; GT persistence; reasons for treatment failure; and content of intravenous bags.
- In Italy, seven of 22 GTs were appraised, but there were no new appraisals since our previous review. Zolgensma® and Strimvelis® mentioned RWE as part of the reviewed evidence, and Tecartus® and Kymriah® did not mention RWE. AIFA[7] requested RWE in two of them (Libmeldy® and Yescarta®).
- In Spain, 11 of 22 GTs were appraised. Out of these, RWE was requested for four of them and was not mentioned in six reports. Five new reports were found since our previous review. Only Abecma® submitted RWE for its assessment.
- In Canada, nine of 22 GTs were appraised. Five were reassessed since our previous review in 2023. Overall, CADTH[10] requested RWE in two HTA reports, while RWE was submitted in the evidence package of six GTs. In the reassessed GT reports, RWE was used to compare the GTs with relevant comparators in real-world clinical practice, or to identify patients from real-world databases.
- In Germany, six therapies were reassessed and RWE was consistently mentioned. Two GTs were appraised for the first time. Four reports used or required observational studies and three mentioned long-term follow-up data, registry data, or observational data. Only Hemgenix® mentioned the EMA's[12] request for observational studies.
- In Japan, no GTs approved were reassessed since our last review. All eight GTs from our original review plus one new GT assessed for a first time mentioned RWE and will be due for reassessment. For most GTs, the Japanese HTA requested a use-results survey or post-marketing use-results survey for the Japanese population.

Gene therapy	APPRAISAL OF GTS WITH RWE SINCE APRIL 2023							
	NICE (UK)	HAS (France)	G-BA (Germany)	AIFA (Italy)	AEMPS (Spain)	ICER (US)	CADTH (Canada)	PMDA (Japan)
Elevidys® (2023)	○	○	○	○	○	○	○	○
Casgevy® (2023)	○	●	○	○	○	◐	○	○
Lyfgenia® (2023)	○	○	○	○	○	◐	○	○
VyJuvek® (2023)	○	○	○	○	○	○	○	○
Hemgenix® (2022)	○	●	◐	○	●	○	◐	○
Adstiladrin® (2022)	○	○	○	○	○	○	○	○
Roctavian® (2022)	○	●	○	○	●	○	○	○
Carvykti® (2022)	○	○	●	○	●	○	◐	○
Skysona® (2022)	○	○	○	○	○	○	○	○
Abecma® (2021)	○	◐	◐	○	◐	○	○	○
Breyanzi® (2021)	○	◐	◐	○	○	○	○	○
Delytact® (2021)	○	○	○	○	○	○	○	○
Libmeldy® (2020)	○	◐	○	○	●	●	○	○
Tecartus® (2020)	◐	◐	◐	○	○	○	◐	○
Zynteglo®** (2022)	○	○	○	○	○	○	○	○
Zolgensma® (2019)	○	◐	●	○	○	○	○	○
Collategene® (2019)	○	○	○	○	○	○	○	○
Luxturna® (2017)	○	○	◐	○	○	○	○	○
Yescarta® (2017)	◐	◐	◐	○	○	○	●	○
Kymriah® (2017)	○	◐	◐	○	○	○	●	○
Strimvelis® (2016)	○	○	●	○	○	○	○	○
Imlygic® (2015)	○	○	○	○	○	○	○	○

Abbreviations: AEMPS = Spanish Agency of Medicines and Medical Devices; AIFA = Italian Medicines Agency; CADTH = Canadian Agency for Drugs and Technologies in Health; G-BA = Federal Joint Committee; GT = gene therapy; HAS = Haute Autorité de santé; HTA = health technology assessment; ICER = Institute for Clinical and Economic Review; NICE = National Institute for Health and Care Excellence; PMDA = Pharmaceutical and Medical Devices Agency; RWE = real-world evidence

*GTs are listed by the year of their initial HTA and/or marketing authorization approval; study includes all HTAs and reassessments 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

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

Discussion

- The last decade saw an evolution in how RWE is being used, especially since transformative and expensive therapies such as GTs have launched in the market. GTs often target rare, severe diseases with small patient populations. This often translates into uncertainty in the evidence and is associated with obvious challenges during an appraisal process and beyond (i.e., at the time of pricing and coverage decisions).
- RWE can help address several of the issues arising from limited evidence packages by tracking long-term outcomes of patients who have received a GT via a registry, providing evidence for indirect comparisons, real-life costs, and more.
- For example, our review found that Canada systematically searches for and implements RWE in its assessments to understand safety and efficacy of GTs and to define which patients might benefit the most from GTs in practice. In Spain, Valtermed has been used to create payment-by-results agreements to allow for early access to innovative, expensive therapies.
- As thinking evolves about new policies to enable access to GTs, RWE will be required to understand factors that inform how HTA recommendations and reimbursement policies for these products should work.
- Several HTA bodies, such as NICE[4], HAS[5,] and CADTH[10], have released frameworks and guidelines for use of RWE. CADTH[10] has also begun offering scientific advice specifically on this topic. However, at the time of this research, there still seems to be heterogeneity on how RWE is used, considered, and appraised during HTA processes.
- In Europe, the EU HTA Regulation could have provided an opportunity to harmonize the use of RWE across Member States. However, the EUnetHTA21 deliverables highlight the preference for the use of randomized evidence and are purposefully vague on potential cases of use for RWE. This is because the deliverables intend to be a guidance for Joint Clinical Assessment (JCA) assessors and co-assessors, as opposed to prescriptive guidelines. In addition to stakeholder engagement (e.g., via integrated scientific advice) to prepare robust submission dossiers, monitoring the outcomes of JCAs in 2025 will be critical to understand how the deliverables are being interpreted by relevant stakeholders in Europe.
- In the US, ICER's[9] value assessment framework includes a section on RWE that highlights its work to incorporate RWE into their reports. However, ICER[9] is an independent organization and payers are not mandated to consider its assessments at the time of making coverage decisions for these transformative and expensive therapies.
- This does not mean there are not opportunities in the US to leverage RWE to generate relevant evidence for decision-makers. Tokenization is a clear example of this, as it allows the linkage of various data sources (e.g., registry data with Medicare costs) to tackle a wide variety of research questions.

Conclusions

- Comparisons with our previous review show increasing interest in RWE to confirm long-term outcomes.
- Approaches/acceptability of RWE vary across HTA bodies.
- GT manufacturers must prepare early by engaging with stakeholders, identifying evidence requirements tailored to markets of interest and developing and implementing an integrated evidence plan.

References

1. https://www.fda.gov/
2. https://www.canada.ca/en/health-canada.html
3. https://www.mhlw.go.jp/English/
4. https://www.nice.org.uk/
5. https://www.has-sante.fr/
6. https://www.g-ba.de/
7. https://www.aifa.gov.it/
8. https://www.aemps.gob.es/
9. https://icer.org/
10. https://www.cadth.ca/
11. https://www.pmda.go.jp/english/index.html
12. https://www.ema.europa.eu/en/homepage

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