Real-World Evidence in Gene Therapies: Recommendations Versus Reality

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PBI44

OBJECTIVES

- To understand whether real-world evidence recommendations, made by regulatory and reimbursement bodies when evaluating gene therapies, are subsequently addressed by manufacturers.

BACKGROUND

- Recent advances in gene therapies have facilitated the generation of effective, novel treatment options for rare and debilitating genetic disorders.[1]
- However, due to the challenges of evidence generation in small, heterogeneous patient populations, manufacturers may face barriers to generating the robust safety and effectiveness data for these novel treatments that regulatory/reimbursement bodies currently expect.[1–3]
- One solution to these challenges may be the collection of real-world data (RWD). RWD are collected outside the context of tightly monitored trials, and are generally reflective of clinical practice and the target population in which the treatment would be used.[4]
- It is widely agreed that manufacturers should use evidence derived from RWD (real-world evidence [RWE]) to supplement trial data in support of regulatory approval and reimbursement.[3]
- Despite this agreement, it is unclear whether RWE is being used to support submissions either proactively or reactively, and whether any recommendations for RWE generation are in fact being implemented.

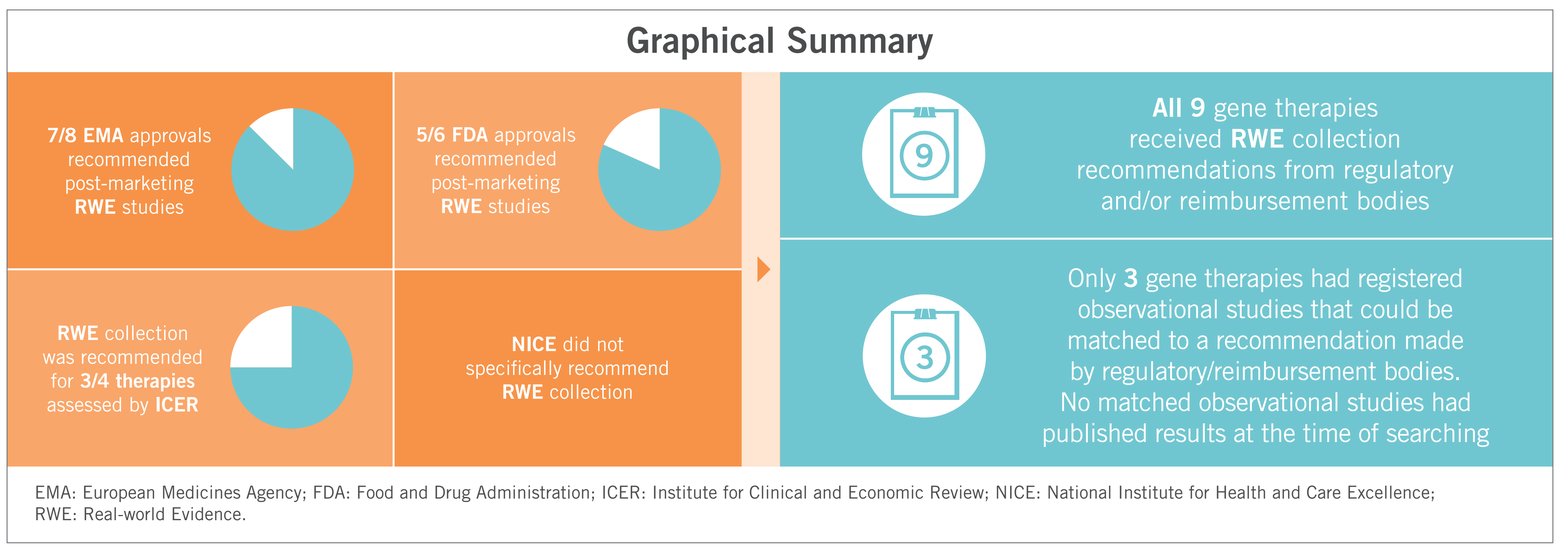
METHODS

- In February 2019, the European Medicines Agency (EMA) and Food and Drug Administration (FDA) websites were searched for regulatory documents using terms for gene therapies.
- The National Institute for Health and Care Excellence (NICE) and Institute for Clinical and Economic Review (ICER) websites were then searched for related appraisals and reviews, respectively, in May 2019.
- The documents retrieved were then searched to identify cases where RWE had been submitted as part of the manufacturer's application.
- Then, instances where collection of additional RWE had been recommended by regulatory/reimbursement bodies in the relevant documents were searched for, and the details extracted.
- ClinicalTrials.gov was searched on 30 May 2019, for any observational studies, including patient registries, using the gene therapy names.
- Finally, results from ClinicalTrials.gov were cross-referenced with the extractions from the regulatory/reimbursement documents through comparison of expected outcomes, patient numbers and study timeframes, in order to establish whether recommendations had been implemented.

RESULTS

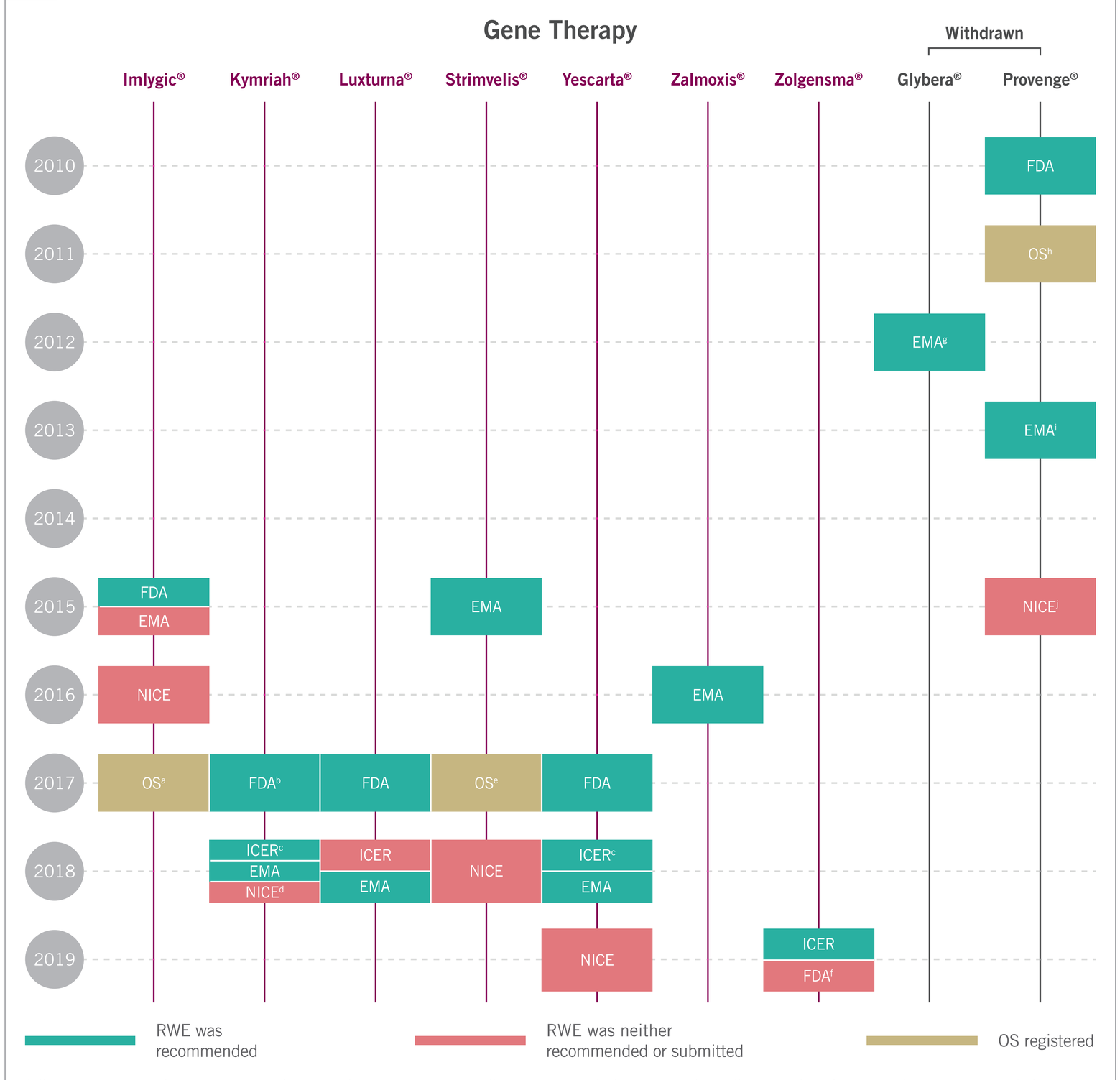
- Nine gene therapies were identified by searches of the EMA and FDA websites; seven in rare diseases and two in oncology. Eight EMA marketing authorisations were found, though one was subsequently withdrawn (Provenge®) and one expired and was not renewed (Glybera®). Six FDA approvals were found, with four gene therapies currently approved by both the EMA and FDA **(Figure 1)**.
- No RWE on the gene therapies was submitted in regulatory applications and a lack of trial data was commonly cited.
- Six related NICE appraisals, corresponding to five gene therapies were identified, however, the NICE submission for Provenge® was subsequently withdrawn. Three ICER reviews were identified.

Graphical Summary



EMA: European Medicines Agency; FDA: Food and Drug Administration; ICER: Institute for Clinical and Economic Review; NICE: National Institute for Health and Care Excellence; RWE: Real-world Evidence.

1 Timeline for recommendation versus implementation of RWE studies for gene therapies



NICE appraisal documents reviewed included the Highly Specialised Technologies Guidance documents, the Evidence Review Group report and the manufactuer's submission. ICER assessments reviewed were the Final Evidence Reports. [a]NCT02910557; [b]Kymriah has been approved by the FDA for use in two different indications, with the first approved in August 2017 and the second in April 2018; [c]A single ICER assessment reviewed both Kymriah and Yescarta in the same document; [d]NICE appraised Kymriah for reimbursement for two different indications, with the first approved in December 2018 and the second in March 2019; [e]NCT03478670; [f]An observational long-term follow-up study to one completed clinical trial in the US was reported to be ongoing, however no results were provided; [g]EMA approval of Glybera® has subsequently expired and was not renewed; [h]NCT01306890; [i]EMA approval for Provenge® has subsequently been withdrawn; [j]Reimbursement of Provenge® by NICE has subsequently been withdrawn. EMA: European Medicines Agency; FDA: Food and Drug Administration; ICER: Institute for Clinical and Economic Review; NICE: National Institute for Health and Care Excellence; OS: observational study.

- No NICE manufacturer submissions included RWE studies reporting clinical outcomes for the identified gene therapies, however RWD inputs were included in all economic models, most commonly for healthcare resource use.
- All of the nine gene therapies received RWE collection recommendations from regulatory and/or, where relevant, reimbursement bodies.
- Despite this, at the time of searching, only three of these products had registered observational studies that could be mapped to a recommendation made by regulatory/reimbursement bodies, of which two were patient registries. However, none had yet reported results (Imlygic®: NCT02910557; Provenge®: NCT01306890; Strimvelis®: NCT03478670).

CONCLUSIONS

- Although regulatory and reimbursement authorities place importance on RWE for gene therapies, few recommended studies could be identified in ClinicalTrials.gov.
- This suggests either barriers to registration of these studies, the use of alternative methods to gather RWE, or that these recommendations are simply not being implemented.
- Facilitation of registration of RWE studies, combined with the introduction of formal re-appraisals may be a potential solution to make these recommendations become reality.

References

1. Abou-El-Enein M, *et al.* EClinicalMedicine 2019;7:13–14; **2.** Elverum K, Whitman M. Delivering cellular and gene therapies to patients: solutions for realizing the potential of the next generation of medicine. Gene Therapy 2019. Available at: https://www.nature.com/articles/s41434-019-0074-7 <https://www.nature.com/articles/s41434-019-0074-7> . [Last accessed 18 September 2019]; **3.** Insitute for Clinical and Economic Review. 2017. GENE THERAPY: Understanding the Science, Assessing the Evidence, and Paying for Value. Available at https://icer-review.org/wp-content/uploads/2017/03/ICER-Gene-Therapy-White-Paper-030317.pdf. [Last accessed 12 September 2019]; **4.** GetReal. Glossary of Definitions of Common Terms. Available at https://www.imi-getreal.eu/Portals/1/Documents/01%20deliverables/D1.3%20-%20Revised%20GetReal%20glossary%20-%20FINAL%20updated%20version_25Oct16_webversion.pdf. [Last accessed 18 September 2019].

Acknowledgements

The authors thank Kevin Racaza, Costello Medical, for graphic design assistance.

Presented at the ISPOR 22nd Annual European Congress | Copenhagen, Denmark | 2–6 November 2019

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