Economic Modelling of Gene Therapies Based on the Comparison of Two Independent Models Assessing Voretigene Neparvovec for RPE65 - Mediated Inherited Retinal Dystrophy

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ISPOR US, Washington, DC
USA Area and Virtual
May 15-18, 2022

EE82

Objectives

- Two different cost-effectiveness models for voretigene neparvovec (Luxturna®) for RPE65 – Mediated Inherited Retinal Dystrophy have been considered in independent evaluations by the Institute for Clinical and Economic Review (ICER) and by National Institute for Health and Care Excellence (NICE). The models differed in structure, parameters, assumptions, and results.
- We sought to compare these models, analyze the use of alternative models for each evaluation and check the impact of key inputs and assumptions on the model results.

Methods

- We replicated both models with the use of MS Excel 2016. The replicated models were validated by comparing their results with published information focusing on the health economic outcomes: costs, QALYs and incremental cost-effectiveness ratio (ICER). To deal with identified replication hurdles some assumptions concerning the model structure and input data were made. Also, in order to better understand the long-term multistate survival approach considered in NICE submission, Markov trace were visualized and adjusted to the original (Figure 1).
- As a next step, the ICER model was adapted to the UK and the model assessed by NICE was run from the US perspective. Because of some discrepancies in model structure and country specific data, not all parameters were adapted. A summary of adapted input data are presented in the Table 1. Since levels of visual impairment were divided into several categories in model assessed by NICE and the cost-effectiveness analysis conducted by ICER track only visual impairment and blindness, differences in cost application based on visual acuity were recognized and transferred into the most appropriate form of visual range.
- No clear evidence on chosen duration of treatment effect, duration of waning period and rate of residual treatment effect was presented in the model documentation. Hence, several assumptions were varied in replicated models to test their impact on the model results.
- Additionally, different survival models reflecting the loss of the treatment effect were tested in the model evaluated by NICE (Figure 2).
- In the ICER economic model, different decline in visual outcomes versus standard of care (SoC) and various duration of treatment effect were tested.

Figure 1. Visualization of Markov trace in replicated model

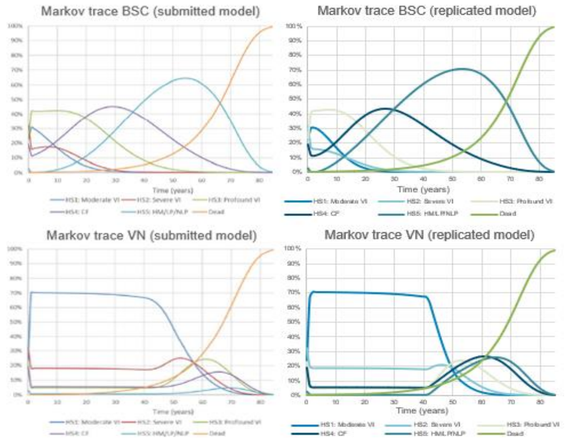
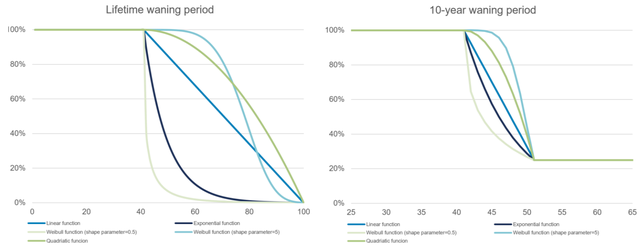


Table 1. Summary of parameters adapted to country settings

	ICER	NICE
Discount rate	3% discount rate for costs and outcomes (QALYs)	3.5% discount rate for costs and outcomes (QALYs)
Costs	• One-time event cost (VN treatment and surgery) • Direct medical costs based on visual acuity (only health care system perspective)	• One-time events costs (acquisition, administration, eligibility testing, monitoring, adverse events) • Long-term resource utilization by age group and health state
	Comment: For NICE adaptation costs were adjusted to five health states impairment classes and converted to LogMAR scale.	*Comment:* For ICER adaptation costs were converted to decimal scale and five VA ranges.
Adverse events	Three AEs associated with VN use (eye irritation, eye pruritius, mascular hole.	Disabilities for 3 AEs (cataract, eye inflammation, increased intraocular pressure) associated with VN use (one-time QALY loss)
Duration of 100% treatment effect	10 – year treatment effect	40 – year treatment effect
Mortality	Gender-specific from United States life tables 2014	General population life tables for England and Wales, based on data for the years 2016-2018

Figure 2. Treatment effect reduction



Results

- Replicated models provided similar results to those reported in the literature. Differences concern mostly the cost estimates in the ICER model and result from lack of sufficient details in the model report on cost inputs (Table 2).
- Adapted models have similar incremental costs to those published; however, a difference is visible in the NICE model adapted to ICER settings.
- There are significant differences in incremental QALYs obtained with the use of adapted models vs. original ones.
- These differences arise mainly from distinct assumptions on the duration of full treatment effect undertaken in both models (10 vs 40 years).
- Interestingly, similar incremental cost-effectiveness ratios have been obtained in both models after their adaptation to alternative settings. It proves that the ICER model tends to be more conservative in comparison to the NICE model.
- Results of the ICER model are also less sensitive on the visual outcome testing.
- On the other hand, analysis of different assumptions concerning reduction of treatment effect in the NICE model showed their significant impact on the model results. (Table 3)

Table 2. Models' comparison

Models' comparison	ICER model			NICE model		
	Inc. costs ($)	Inc. QALYs	ICER	Inc. costs (£)	Inc. QALYs	ICER
Published results	$825,621	1.3	$643,813	£612,013	7.1	£86,635
Replicated model	$773,522	1.3	$586,027	£611,817	7.0	£87,742
Adapted	NICE model with ICER settings			ICER model with NICE settings		
	$945,165	2.7	$345,436	£605,756	1.6	£388,818

Table 3. Analysis of different assumptions concerning reduction of treatment effect in the NICE model

Arm	Costs	QALYS	Inc. Costs	Inc. QALYs	ICER
40-year treatment effect, 10-year treatment waning period from 100% to 25% (Linear function)					
BSC	£45,830	3.4	£611,817	7.0	£87,742
VN	£657,648	10.4			
20-year treatment effect, 10-year treatment waning period from 100% to 25% (Linear function)					
VN	£659,579	8.3	£613,749	4.9	£125,435
20-year treatment effect, 10-year treatment waning period from 100% to 25% (Exponential function)					
VN	£659,622	8.2	£613,791	4.8	£127,136
20-year treatment effect, 10-year treatment waning period from 100% to 25% (Weibull function, shape parameter=0.5)					
VN	£659,705	8.1	£613,874	4.7	£130,515
20-year treatment effect, 10-year treatment waning period from 100% to 25% (Weibull function, shape parameter=5)					
VN	£659,473	8.5	£613,643	5.1	£121,386
20-year treatment effect, 10-year treatment waning period from 100% to 25% (Quadratic function)					
VN	£659,514	8.4	£613,684	5.0	£122,938
20-year treatment effect, lifetime waning period from 100% (Linear function)					
VN	£659,408	8.6	£613,578	5.2	£118,759
20-year treatment effect, lifetime waning period from 100% (Exponential function)					
VN	£659,719	8.1	£613,889	4.7	£131,252
20-year treatment effect, lifetime waning period from 100% (Weibull function, shape parameter=0.5)					
VN	£659,834	7.9	£614,003	4.5	£136,303
20-year treatment effect, Lifetime waning period from 100% (Weibull function, shape parameter=5)					
VN	£659,344	8.7	£613,513	5.3	£116,415
20-year treatment effect, Lifetime waning period from 100% (Quadratic function)					
VN	£659,353	8.7	£613,522	5.3	£116,752
10-year treatment effect, 10-year treatment waning period from 100% to 25% (Linear function)					
VN	£660,542	6.5	£614,712	3.0	£201,923
10-year treatment effect, 10-year treatment waning period from 100% to 25% (Exponential function)					
VN	£660,603	6.4	£614,773	3.0	£208,294
10-year treatment effect, 10-year treatment waning period from 100% to 25% (Weibull function, shape parameter=0.5)					
VN	£660,720	6.2	£614,890	2.8	£221,622
10-year treatment effect, 10-year treatment waning period from 100% to 25% (Weibull function, shape parameter=5)					
VN	£660,392	6.7	£614,561	3.3	£187,607
10-year treatment effect, 10-year treatment waning period from 100% to 25% (Quadratic function)					
VN	£660,450	6.6	£614,620	3.2	£192,961
10-year treatment effect, lifetime waning period from 100% (Linear function)					
VN	£660,248	6.9	£614,454	3.5	£176,467
10-year treatment effect, lifetime waning period from 100% (Exponential function)					
VN	£660,860	5.9	£615,030	2.5	£243,269
10-year treatment effect, lifetime waning period from 100% (Weibull function, shape parameter=0.5)					
VN	£661,008	5.7	£615,178	2.3	£267,014
10-year treatment effect, Lifetime waning period from 100% (Weibull function, shape parameter=5)					
VN	£660,308	6.8	£614,478	3.4	£180,146
10-year treatment effect, Lifetime waning period from 100% (Quadratic function)					
VN	£660,215	7.0	£614,384	3.6	£170,859

CONCLUSIONS

- The way of modelling can differ between countries and significantly impact the economic evaluation.
- This is of particular importance for gene therapies which are characterized with high and often curable benefits which need to be extrapolated to the long term based on clinical studies with short follow-up durations.
- The key areas of uncertainty are related to duration of treatment effect, waning period and rate of residual treatment effect.

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