Are HTA Bodies Responding to the Assessment Challenges Posed by Cell and Gene Therapies?

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Background and objectives

- Cell and gene therapies pose several additional challenges for HTA
- These include: difficulties in undertaking clinical assessments and in considering any additional elements of economic value for these therapies
- These issues may not require a completely new reference case for HTA, but make require additional attention[1]
- The objective of this study was to assess the extent to which HTA bodies are responding to these challenges

1. Drummond, MF *et al Value in Health* 2019,;22(6): 661-668

Methods

- Targeted review of the clinical and economic aspects of cell and gene therapy, based on a 'pearl-growing' approach based on the Drummond *et al* (2019) paper
- Detailed review of HTA reports, using the checklist developed by Drummond *et al* (2019)
- Policy Forum, to discuss the findings, including decision-makers and patient and industry representatives

Checklist For Assessing Gene Therapies

Item	Yes	No	Notes
Clinical effectiveness			
Surrogate endpoint used	☐	☐	Validation given?
Rare disease	☐	☐	Prevalence _____
Serious condition	☐	☐	
Single-arm trial	☐	☐	Matched historical cohort used?
Pediatric population	☐	☐	Age range _____
Reporting of adverse consequences and risks	☐	☐	
Size of clinical trial	____ number of patients		
Length of clinical trial	____ duration in months		
Extrapolation to long-term outcomes	____ duration in months		
	Yes	No	Quantification
Elements of value			
Severe disease	☐	☐	
Value to caregivers	☐	☐	
Insurance value	☐	☐	
Scientific spillovers	☐	☐	
Lack of alternatives	☐	☐	
Substantial improvement in life expectancy	☐	☐	
	Yes	No	Notes
Other considerations			
Discounting			
Different discount rates explored	☐	☐	
Uncertainty			
Alternative payment models explored	☐	☐	

Drummond M et al. Value in Health. 2019;22(6):661-668

CELL AND GENE THERAPIES CONSIDERED

Kymriah	relapsed or refractory diffuse large b-cell lymphoma
Kymriah	relapsed or refractory b-cell acute lymphoblastic leukaemia
Yescarta	diffuse large b-cell lymphoma and primary mediastinal b-cell lymphoma
Luxturna	inherited retinal dystrophies caused by rpe65 gene mutations
Strimvelis	severe combined immunodeficiency caused by adenosine deaminase deficiency
Imlygic	unresectable metastatic melanoma
Alofisel	perianal fistula in Crohn's disease
Provenge*	*metastatic hormone-relapsed prostate cancer*
Glybera*	*lipoprotein lipase deficiency*
Zolgensma	spinal muscular atrophy

* Withdrawn from the market

HTA REPORTS ANALYSED

	NICE (UK)	ICER (US)	CADTH (CA)	SMC (UK)	AIFA (IT)	HAS (FR)	G-BA (DE)	AEMPS (ES)
Kymriah DLBCL	X			X	X	X	X	X
Kymriah ALL	X	X			X	X	X	X
Yescarta	X	X		X	X	X	X	X
Luxturna	X	X	X	X		X	X	X
Strimvelis	X							
Imlygic	X						X	X
Alofisel	X			X		X	X	X
Provenge	X						X	
Glybera						X	X	
Zolgensma	X	X	X	X	X	X	X	

AEMPS = Agencia Española de Medicamentos y Productos Sanitarios; AIFA = Agenzia Italiana del Farmaco; ALL = acute lymphoblastic leukaemia; CADTH = Canadian Agency for Drugs and Technologies in Health; DLBCL = diffuse large b-cell lymphoma; G-BA = Gemeinsame Bundesausschuss; HAS = Haute Autorité de Santé; ICER = Institute for Clinical and Economic Review; NICE = National Institute for Health and Clinical Excellence; SMC = Scottish Medicines Consortium

Results

- Extent of recognition of challenges in the clinical data
- Extent of consideration of additional elements of value
- Views of HTA bodies on (i) deficiencies in the clinical data, and (ii) the importance of the various elements of value

	Kymriah DLBCL (N = 6)	Kymriah ALL (N = 6)	Yescarta (N = 7)	Luxturna (N = 7)	Strimvelis (N = 1)	Imlygic (N = 3)	Alofisel (N = 5)	Provenge* (N = 2)	Glybera* (N = 2)	Zolgensma (N = 7)
Surrogate endpoint used	Yes (5)	Yes (5)	Yes (6)	Yes (6)	Yes (1)	Yes (2)	Yes (4)	No (2)	Yes (1)	Yes (2)
Rare disease	Yes (3)	Yes (3)	Yes (4)	Yes (7)		No (1)	Yes (4)	No (2)	Yes (2)	Yes (7)
Serious condition	Yes (5)	Yes (5)	Yes (6)	Yes (6)	Yes (1)	Yes (2)	Yes (4)			Yes (6)
Single-arm trial	Yes (6)	Yes (6)	Yes (7)	No (7)	Yes (1)	No (3)	No (5)	No (2)	Yes (2)	Yes (7)
Pediatric population	No (6)	Yes (5)	No (7)	Yes (2)	Yes (1)	No (3)	No (5)	No (2)	No (2)	Yes (7)
Reporting of adverse consequences and risks	Yes (6)	Yes (6)	Yes (7)	Yes (7)	Yes (1)	Yes (2)	Yes (5)	Yes (2)	Yes (1)	Yes (7)
Size of clinical trial (number of patients)	99-167	58-97	111	29-31	18	436	212-289	512	27	15-33
Length of clinical trial (months)	13.9-40.3	8.7-30.2	8.7-27.1	12-48		48	12-24	20.6-34	<12	12-53
Extrapolation to long-term outcomes (months)	552	>1000	528			360	480	120		924

* Withdrawn from the market

REFERENCES TO ELEMENTS OF VALUE IN HTA REPORTS FOR ONASEMNOGENE ABEPARVOVEC (ZOLGENSMA)

ELEMENT	NICE	ICER	CADTH	SMC	AIFA	HAS	G-BA
Severe disease	Yes	Yes	Yes	Yes	Yes	Yes	N/A
Value to caregivers	Yes	Yes	Yes	Yes	N/A	Yes	N/A
Insurance value	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Scientific spillovers	Yes	N/A	N/A	N/A	N/A	N/A	N/A
Lack of alternatives	No	No	No	No	No	No	N/A
Substantial improvement in life expectancy	Yes	Yes	Yes	Yes	Yes	Yes	N/A
Discounting	Yes	Yes	N/A	Yes	Yes	Yes	N/A
Different discount rates explored	Yes	Yes	N/A	Yes	Yes	Yes	N/A
Uncertainty	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Alternative payment models explored	No	N/A	No	No	Yes	N/A	N/A

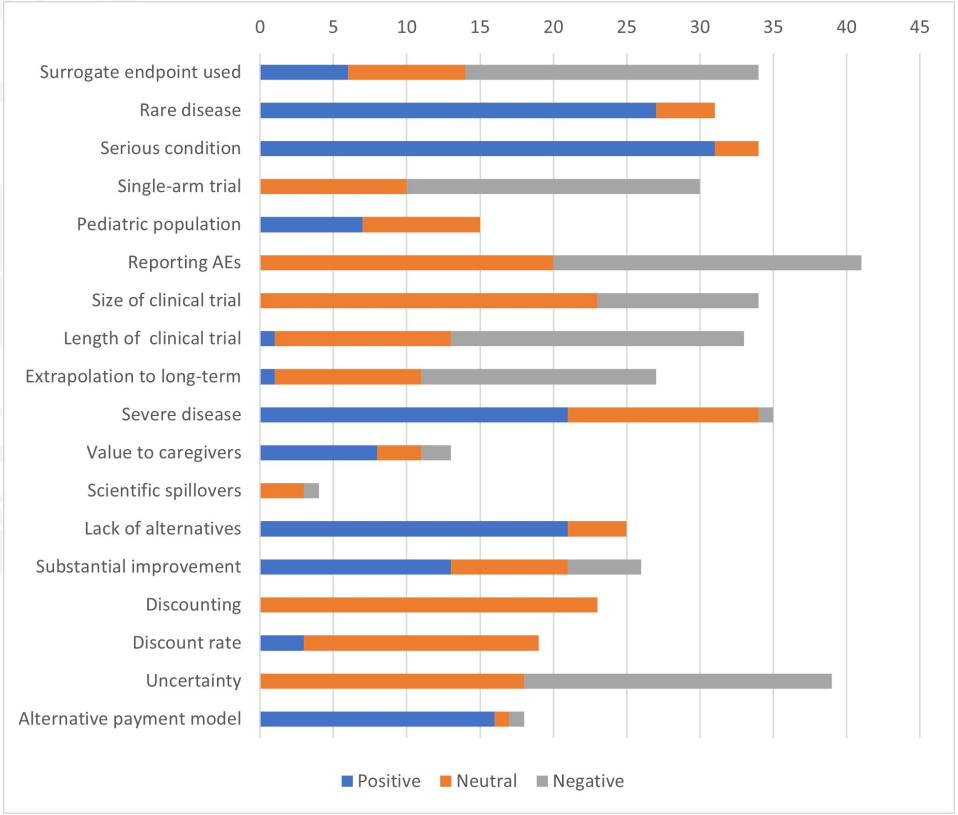
DETAILS OF REFERENCES TO ECONOMIC ELEMENTS BY NICE (ZOLGENSMA)

Element	Yes	No	Notes
Severe disease	X		The authority recognized the severity of the disease and its fatality if treated with best supportive care.
Value to caregivers	X		No explicit quantification. The manufacturer and patient organizations claimed a significant burden on caregivers and that the treatment, by improving infants' autonomy, could increase the likelihood of labor market participation for parents. The authority did not dispute the claim.
Insurance value		N/A	N/A
Scientific spillovers	X		No explicit quantification. The manufacturer claimed the treatment will lead to greater understanding of epidemiology, pathology and management of the condition and opportunities for treatment optimization. The authority did not dispute the claim.
Lack of alternatives		X	Nusinersen is an alternative; it was underlined that it does not represent established clinical practice in the UK yet.
Discounting	X		3.5% for costs.
Different discount rates explored	X		N/A
Uncertainty	X		Deterministic, probabilistic, and scenario-based sensitivity analyses.
Alternative payment models explored		X	The manufacturer proposed a confidential simple discount on the published UK list price.

SUMMARY STATISTICS: ELEMENTS OF VALUE

ELEMENT	CONSIDERED RELEVANT No. (% of reports)
Severe disease	35 (76%)
Value to caregivers	14 (30%)
Insurance value	0 (0%)
Scientific spillovers	3 (7%)
Lack of alternatives	24 (52%)
Substantial improvement in life expectancy	24 (52%)
Discounting	23 (50%)
Different discount rates explored	17 (37%)
Uncertainty	42 (91%)
Alternative payment models explored	12 (26%)

Views of HTA bodies on the various considerations



Discussion and Conclusions

- Most of the deficiencies in the clinical data were being considered
- Consideration of the various elements of value was more variable
- Main clinical concerns were:
  - use of surrogate endpoints
  - single arm trials
  - short term studies and possible long-term adverse effects
- Most recognition of potential additional value was:
  - treatment of severe disease
  - lack of treatment alternatives
  - substantial improvement in health

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