Understanding the Application of Various Statistical Analysis Methods to Inform Comparative Effectiveness of Ultra Orphan Treatments: A Review of NICE HST Guidance

HTA316

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INTRODUCTION

- National Institute for Health and Care Excellence (NICE) evaluates medicines for ultra rare diseases, having a prevalence <1 per 50,000 persons, by the Highly Specialised Technologies (HST) evaluation process

OBJECTIVE

- To understand the role of different statistical analysis methods used to inform the comparative effectiveness of ultra orphan treatments

METHODS

- Manufacturer submissions, ERG reports, and final appraisal documents were reviewed for all HST submissions till June 2023
- The review assessed the clinical evidence and statistical analyses submitted by the manufacturers
- Final recommendations based on the assessment of the clinical evidence, statistical analyses, and ERG comments were also reviewed

RESULTS

- Twenty-three HSTs with final recommendation were identified (Table 1)
- Majority of the guidance (61%) were focused on endocrine, nutritional, and metabolic rare diseases
- All submissions received positive recommendations. However, it is important to note that a simple discount-based patient access scheme was included with all recommendations
- The clinical evidence included in the submissions comprised of RCTs (56%), single arm trials (69%), non-RCTs (8%) and observational studies (17%) (Figure 1)
- Overall, 22% submissions included pooled analyses followed by inclusion of a naïve indirect comparison in 17% submissions (Figure 2)
- Mostly population-adjusted indirect comparisons were not performed due to lack of relevant clinical data, heterogeneity of the included studies and non-availability of comparator data
- In two submissions, an MAIC was attempted but was deemed infeasible due to small effective sample size and lack of covariates for adjustment
- In 22% submissions, ERG recommended to conduct additional population-adjusted analyses to support the clinical effectiveness and reduce the uncertainty around submitted evidence

Figure 1: Types of study designs involved

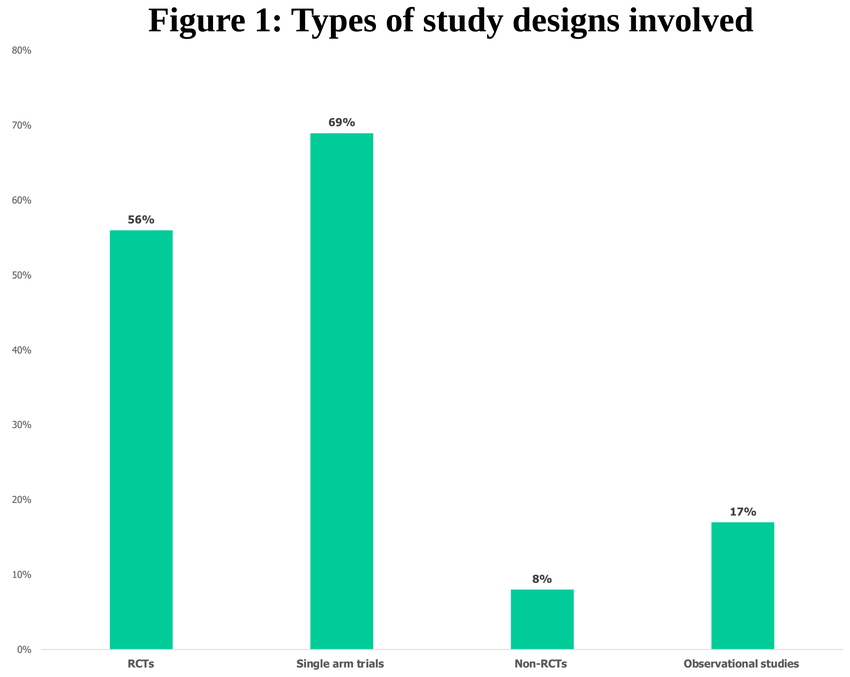

Figure 2: Statistical methods

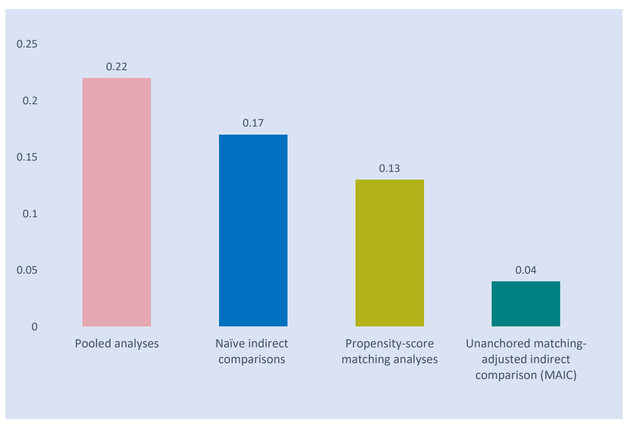

Table 1: Overview of NICE Highly Specialised Technology (HST) Appraisals

Guidance no.	Title	Date	Therapeutic area by ICD-codes	Intervention	Final recommendation	Any analysis included? Name, if yes	Any analysis recommended by ERG
HST24	Onasemnogene abeparvovec for treating presymptomatic spinal muscular atrophy	19-Apr-23	Muscular Atrophy, Spinal	Onasemnogene abeparvovec	Recommended with restriction	No	No
HST15	Onasemnogene abeparvovec for treating spinal muscular atrophy	07-Jul-21	Muscular Atrophy, Spinal	Onasemnogene abeparvovec	Recommended with restriction	Naïve comparison	No
HST26	Eladocagene exuparvovec for treating aromatic L-amino acid decarboxylase deficiency	19-Apr-23	Endocrine, nutritional and metabolic diseases	Eladocagene exuparvovec	Fully recommended	Naïve comparison	No
HST25	Lumasiran for treating primary hyperoxaluria type 1	19-Apr-23	Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	Lumasiran	Fully recommended	No	MAIC
HST23	Asfotase alfa for treating paediatric-onset hypophosphatasia	01-Mar-23	Endocrine, nutritional and metabolic diseases	Asfotase alfa	Recommended with restriction	Pooled analysis	Pooled analysis using retrospective data
HST22	Ataluren for treating Duchenne muscular dystrophy with a nonsense mutation in the dystrophin gene	22-Feb-23	Nervous system	Ataluren	Recommended with restriction	Propensity score matching ITC	No
HST21	Setmelanotide for treating obesity caused by LEPR or POMC deficiency	06-Jul-22	Endocrine, nutritional and metabolic diseases	Setmelanotide	Fully recommended	No	No
HST20	Selumetinib for treating symptomatic and inoperable plexiform neurofibromas associated with type 1 neurofibromatosis in children aged 3 and over	05-May-22	Congenital malformations, deformations and chromosomal abnormalities	Selumetinib	Fully recommended	Naïve comparison	No
HST19	Elosulfase alfa for treating mucopolysaccharidosis type 4A	20-Apr-22	Endocrine, nutritional and metabolic diseases	Elosulfase alfa	Fully recommended	Pooled analysis	Propensity score matching analysis
HST18	Atidarsagene autotemcel for treating metachromatic leukodystrophy	28-Mar-22	Endocrine, nutritional and metabolic diseases	Atidarsagene autotemcel	Recommended with restriction	Pooled analysis	No
HST17	Odevixibat for treating progressive familial intrahepatic cholestasis	22-Feb-22	Digestive system	Odevixibat	Recommended with restriction	MAIC	MAIC
HST16	Givosiran for treating acute hepatic porphyria	24-Nov-21	Endocrine, nutritional and metabolic diseases	Givosiran	Recommended with restriction	No	No
HST14	Metreleptin for treating lipodystrophy	24-Feb-21	Endocrine, nutritional and metabolic diseases	Metreleptin	Fully recommended	MAIC	MAIC
HST13	Volanesorsen for treating familial chylomicronaemia syndrome	21-Oct-20	Endocrine, nutritional and metabolic diseases	Volanesorsen	Fully recommended	No	No
HST12	Cerliponase alfa for treating neuronal ceroid lipofuscinosis type 2	27-Nov-19	Endocrine, nutritional and metabolic diseases	Cerliponase alfa	Recommended with restriction	Pooled analysis	No
HST11	Voretigene neparvovec for treating inherited retinal dystrophies caused by RPE65 gene mutations	09-Oct-19	Eye and adnexa	Voretigene neparvovec	Fully recommended	No	No
HST10	Patisiran for treating hereditary transthyretin amyloidosis	14-Aug-19	Endocrine, nutritional and metabolic diseases	Patisiran	Fully recommended	No	No
HST9	Inotersen for treating hereditary transthyretin amyloidosis	22-May-19	Endocrine, nutritional and metabolic diseases	Inotersen	Fully recommended	No	No
HST8	Burosumab for treating X-linked hypophosphataemia in children and young people	10-Oct-18	Endocrine, nutritional and metabolic diseases	Burosumab	Recommended with restriction	Naïve comparison	No
HST7	Strimvelis for treating adenosine deaminase deficiency–severe combined immunodeficiency	07-Feb-18	Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	Strimvelis	Fully recommended	Pooled analysis	No
HST5	Eliglustat for treating type 1 Gaucher disease	28-Jun-17	Endocrine, nutritional and metabolic diseases	Eliglustat	Fully recommended	No	No
HST4	Migalastat for treating Fabry disease	22-Feb-17	Endocrine, nutritional and metabolic diseases	Migalastat	Fully recommended	No	No
HST1	Eculizumab for treating atypical haemolytic uraemic syndrome	28-Jan-15	Blood and blood-forming organs and certain disorders involving the immune mechanism	Eculizumab	Fully recommended	No	No

CONCLUSION

- A high clinical uncertainty was observed in majority of the HST submissions. A few submissions included pooled analyses, propensity score matching analyses, and naïve comparisons to support clinical effectiveness
- Advanced methods like MAIC, simulated treatment comparison (STC), and multi-level-network meta-regression (ML-NMR) could not be utilised due to smaller sample size and lack of covariate suitable for matching/adjustments

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None