HTA24

What Key Areas of Clinical and Economic Uncertainty Have Scottish Medicines Consortium (SMC) Identified in Ultra-Orphan Initial Assessments to Date?

Bolan F,[1] Popat S,[2] Haria K[2]

[1]Costello Medical, Manchester, UK; [2]Costello Medical, London, UK

Objective

In order to allow manufacturers of ultra-orphan medicines to better prepare for Scottish reimbursement submissions and the post-submission data collection phase, we aimed to identify key areas of clinical and economic uncertainty highlighted by Scottish Medicines Consortium (SMC) to date in their initial assessments within the ultra-orphan pathway.

Background

- Since 2018, SMC has assessed medicines for very rare conditions via the ultra-orphan pathway. To receive ultra-orphan validation, the following criteria must be met:[1]
  - The condition has a prevalence of ≤1:50,000 in Scotland, is chronic and severely disabling and requires highly specialised management, and
  - The medicine has an orphan marketing authorisation from the Medicines and Healthcare products Regulatory Agency.
- Upon the manufacturer's submission of the evidence dossier for an ultra-orphan medicine, SMC conduct an initial assessment of the clinical- and cost-effectiveness of the medicine and report key clinical and economic uncertainties, to inform the data collection stage (**Figure 1**).

Methods

- All published initial assessment reports of medicines in SMC's ultra-orphan pathway up to May 2024 were retrieved from the SMC website.
- Assessments were categorised based on the indicated patient population (adult vs paediatric), disease area and type of medicine considered.
- Areas of uncertainty were extracted and a thematic analysis was conducted. Associations between clinical and economic uncertainties were investigated by counting the number of assessments with both uncertainty categories identified.

Results

- Initial assessments were available for 12 medicines in the ultra-orphan pathway, at the time of analysis (**Table 1**).
- The 12 assessments spanned a range of patient populations, disease areas and medicine types (**Figure 2**).
- Areas of **clinical uncertainty** (**Figure 3a**) most commonly related to the clinical study design and robustness of treatment effect (n=12/12 appraisals, each).
- In **economic evaluations** (**Figure 3b**), uncertainties commonly related to clinical data, modelling approach, health-related quality of life inputs (e.g. methods to estimate utilities) and cost-benefit conclusions.
- There were no clear differences in the frequency at which categories of uncertainties were highlighted by SMC between patient populations, disease areas and medicine types. This demonstrates the almost ubiquitous challenges associated with medicines for ultra-orphan diseases (**QR code**).
- Areas of clinical and economic uncertainty within each initial assessment were frequently linked, with uncertainty in the clinical study design often impacting the assessment of the cost-effectiveness analysis (e.g. clinical data inputs and assumptions) (**Figure 4**).

Conclusion

All SMC ultra-orphan initial assessments highlighted multiple areas of uncertainty in both the clinical and economic evidence, reflecting common challenges with generating robust evidence and demonstrating clinical and cost effectiveness in ultra-orphan diseases. Understanding areas of uncertainty highlighted by SMC may help manufacturers of ultra-orphan disease medicines better and more proactively prepare for the ultra-orphan pathway and inform data collection strategies. Future evaluation of how, and to what extent, uncertainties are addressed by manufacturers during the data collection period and re-assessed by SMC will be valuable.

FIGURE 1

SMC ultra-orphan assessment pathway

FIGURE 2

Characteristics of identified assessments (N=12)

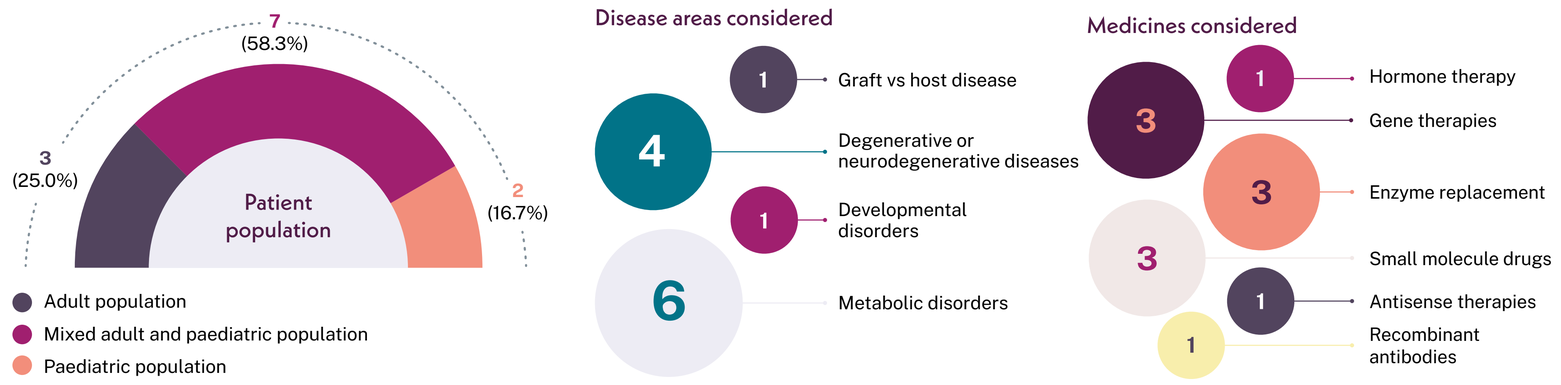


TABLE 1

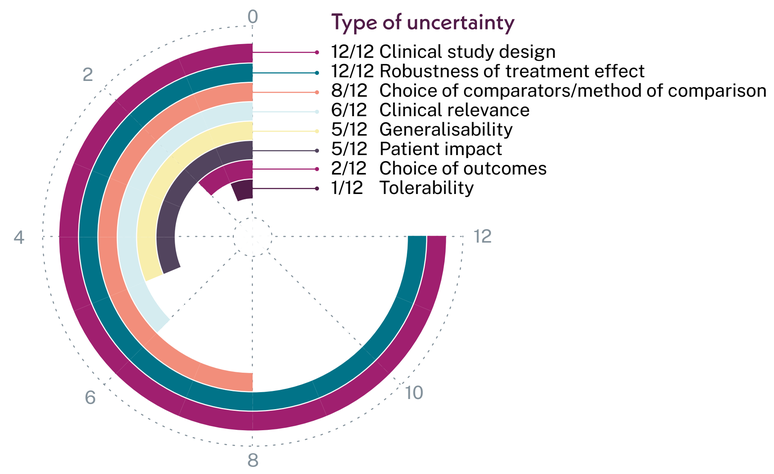
Summary of identified assessments

SMC ID	Medicine	Indication
SMC2228	Voretigene neparvovec (Luxturna®)	Vision loss due to inherited retinal dystrophy
SMC2286	Cerliponase alfa (Brineura®)	CLN2 disease (TPP1 deficiency)
SMC2299	Volanesorsen (Waylivra®)	FCS patients at high risk for pancreatitis
SMC2327	Ataluren (Translarna®)	DMD resulting from a nonsense mutation in the dystrophin gene
SMC2411	Odevixibat (Bylvay®)	PFIC
SMC2413	Atidarsagene autotemcel (Libmeldy®)	MLD characterised by biallelic mutations in the *ARSA* gene
SMC2466	Velmanase alfa (Lamzede®)	Mild to moderate alpha-mannosidosis
SMC2514	Burosumab (Crysvita®)	X-linked hypophosphataemia
SMC2560	Olipudase alfa powder (Xenpozyme®)	Non-CNS manifestations of ASMD in patients with type A/B or type B
SMC2559	Metreleptin powder (Myalepta®)	LD patients with Berardinelli-Seip syndrome, Lawrence syndrome or Barraquer-Simons syndrome
SMC2583	Belumosudil (Rezurock®)	Chronic GvHD
SMC2586	Eladocagene exuparvovec (Upstaza®)	AADC deficiency with a severe phenotype

FIGURE 3

Areas of uncertainty identified by SMC

A. Clinical uncertainties



B. Economic uncertainties

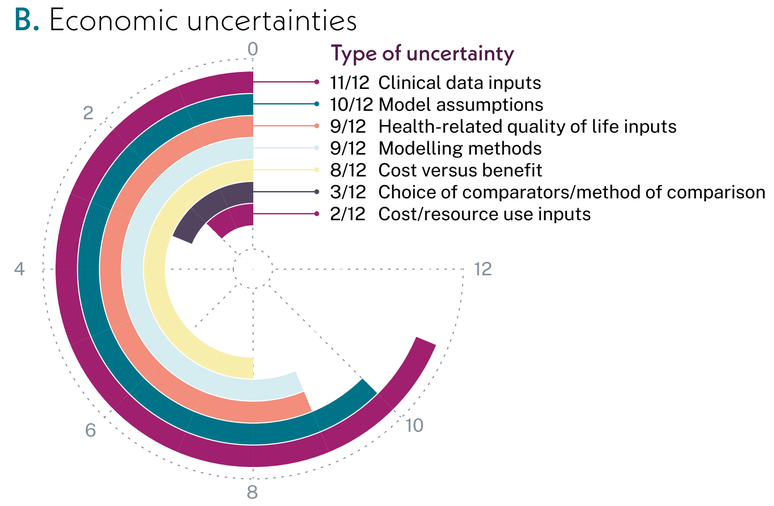


FIGURE 4

Links between areas of clinical and economic uncertainty in the N=12 assessments

Values represent the number of assessments with both uncertainty categories identified		Economic uncertainty categories: Clinical data inputs	Assumptions	HRQoL data inputs	Model design	Cost vs benefit	Comparators/ methods of comparison	Resource use inputs
Clinical uncertainty categories	Clinical study design	11	10	10	9	8	4	2
	Robustness of treatment effect	11	10	10	9	8	4	2
	Comparators/methods of comparison	8	8	7	6	5	4	2
	Clinical relevance	6	6	6	5	4	3	1
	Patient impact	5	4	5	4	4	2	2
	Generalisability	4	4	3	4	2	2	0
	Outcomes	2	2	2	2	2	0	0
	Tolerability	1	0	1	1	1	0	0

Abbreviations: AADC: aromatic L-amino acid decarboxylase; **ARSA:** arylsulfatase A; **ASMD:** acid sphingomyelinase deficiency; **CLN2:** neuronal ceroid lipofuscinosis type 2; **CNS:** central nervous system; **DMD:** Duchenne muscular dystrophy; **FCS:** familial chylomicronemia syndrome; **GvHD:** graft vs host disease; **LD:** leptin deficiency; **MLD:** metachromatic leukodystrophy; **PFIC:** progressive familial intrahepatic cholestasis; **SMC:** Scottish Medicines Consortium; **TPP1:** tripeptidyl peptidase 1.

References: [1]Scottish Medicines Consortium. Ultra-orphan medicine definition. Available at: www.scottishmedicines.org.uk/how-we-decide/ultra-orphan-medicines-for-extremely-rare-conditions/ [Last accessed 09 Sep 24]. **Acknowledgements:** The authors thank Ashleigh Farthing and Mark Tassell, Costello Medical, for graphic design assistance.

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Supplementary material

SUPPLEMENTARY TABLE 1

Uncertainties identified by SMC based on patient population

	Patient population		
	Adult	Paediatric	Mixed adult and paediatric
Total	10	9	7
Clinical uncertainties			
Clinical study design	10	9	7
Robustness of treatment effect	10	9	7
Comparators/methods of comparison	8	7	6
Clinical relevance	6	6	6
Generalisability	4	3	2
Patient impact	4	4	3
Outcomes	2	2	2
Tolerability	1	0	0
Economic uncertainties			
Clinical data inputs	9	9	7
Assumptions	8	8	6
HRQoL data inputs	8	8	6
Model design	8	7	6
Cost vs benefit	6	6	4
Comparators/methods of comparison	4	4	4
Resource use inputs	1	2	1

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SUPPLEMENTARY TABLE 2

Uncertainties identified by SMC based on disease area

	Disease area			
	Metabolic disorder	Degenerative	Developmental	Graft vs host disease
Total	6	4	1	1
Clinical uncertainties				
Clinical study design	6	4	1	1
Robustness of treatment effect	6	4	1	1
Comparators/methods of comparison	5	2	1	1
Clinical relevance	4	2	0	0
Generalisability	2	1	1	1
Patient impact	3	2	0	0
Outcomes	1	1	0	0
Tolerability	1	0	0	0
Economic uncertainties				
Clinical data inputs	5	4	1	1
Assumptions	5	4	1	0
HRQoL data inputs	6	4	0	0
Model design	5	2	1	1
Cost vs benefit	4	4	0	0
Comparators/methods of comparison	3	0	0	1
Resource use inputs	1	1	0	0

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SUPPLEMENTARY TABLE 3

Uncertainties identified by SMC based on medicine type

	Medicine type					
	Gene therapy	Enzyme replacement	Small molecule drug	Hormone therapy	Recombinant antibody	Antisense therapy
Total	3	3	3	1	1	1
Clinical uncertainties						
Clinical study design	3	3	3	1	1	1
Robustness of treatment effect	3	3	3	1	1	1
Comparators/methods of comparison	2	2	3	1	1	0
Clinical relevance	1	2	2	1	0	0
Generalisability	1	1	2	0	1	0
Patient impact	2	1	0	1	0	1
Outcomes	1	1	0	0	0	0
Tolerability	0	0	0	0	0	1
Economic uncertainties						
Clinical data inputs	3	3	3	1	0	1
Assumptions	3	3	2	1	1	0
HRQoL data inputs	2	3	2	1	1	1
Model design	2	3	2	1	0	1
Cost vs benefit	2	3	1	0	1	1
Comparators/methods of comparison	0	1	2	1	0	0
Resource use inputs	1	0	0	1	0	0

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