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PROJECT HERCULES: A case study in developing a multi-company, flexible cost-effectiveness model in a rare disease

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Background

- Duchenne muscular dystrophy (DMD) is an X-linked muscular dystrophy, affecting mainly boys. It is the most rapidly progressive muscular dystrophy; most boys lose the ability to walk by 12 years of age and require ventilatory assistance by the age of 25 [1].
- Treatment options are limited; the mainstay of treatment comprises oral corticosteroids (OCS). However, only 10-40% of patients with DMD survive to age 40 [2, 3]. As such, there remains an unmet need for treatments that slow or halt disease progression.
- A diverse and promising pipeline of treatments is in development. However health technology assessment (HTA) is a key hurdle to market access for new therapies. This hurdle is particularly challenging in rare diseases due to a paucity of data to inform cost-effectiveness models.
- Project HERCULES is an international collaboration between Duchenne UK and eight pharmaceutical companies. This initiative set out to help bring effective new treatments to patients by developing a robust disease level cost-effectiveness model to support HTA submissions.
- It is anticipated that a core disease level model will improve the probability of a positive recommendation from HTA bodies. It will use the best-available data to inform model outcomes, collected and reported in a transparent manner. Additionally, it should reduce the time taken to reach a decision by ensuring future HTAs use a common framework, familiar to all stakeholders.

Objective

- To develop a core disease level cost-effectiveness model
- To capture the natural history of DMD and all potential effects of future treatments
- To incorporate flexibility to account for different interventions and decision problems
- To avoid disclosure of confidential information or breach competition rules due to the collaborative nature of the initiative

Methods

- A multi-state cohort model was developed with health states informed by clinicians, a patient and caregivers.
- Data were collected and synthesised to provide a core data set for natural history, resource use and costs, and health state utilities.
- To avoid the need to share commercially sensitive information on pipeline products, contributing manufacturers and clinical experts discussed all possible treatment effects of future therapies in DMD.
- Manufacturers, HTA experts and health economists identified the characteristics of a therapy, decision problem and audience that would necessitate flexibility within the core model.
- Manufacturers also had the opportunity for one-to-one discussions to ensure the model met their individual needs.

Results

- **Table 1** summarises the areas of flexibility included in the core model.

Table 1: Areas of model flexibility

Population	Intervention	Comparators	Model outcomes	Model settings
• Ability to define patient characteristics at baseline, e.g. age, level of disease progression, mutation & steroid use	Ability to define: • Different types of treatment • Different treatment regimens • Different adverse events • Different treatment effects	• Ability to include current natural history and the impact of new comparators	• Ability to select from different types of analysis (CUA, CEA, CCA)	Ability to define: • Cycle length • Time horizon • Discount rates • Perspectives (healthcare or societal)

Abbreviations: CCA, cost-consequence analysis; CEA, cost-effectiveness analysis; CUA, cost-utility analysis.

- Key areas of flexibility pertain to differences in the interventions evaluated. This includes differences in treatment modalities, regimens and treatment effects **(Table 2).**

Table 2: Flexibility to define different interventions

Treatment modalities	Treatment regimens	Treatment effects
• E.g. Oral and gene therapies	• One-off treatments • Treatments administered at defined disease stages • Treatments of a fixed duration	• Managing symptoms ° Reduction or avoidance of OCS use and/or avoidance of adverse or acute events • Slowing progression • Halting progression • Improvement in function loss or cure (regenerative therapies)

- Table 3 summarises the treatment effects that can be defined for the intervention and comparator. Depending on the treatment effect selected, the user will define a duration of improvement, stabilisation and/or slowing of progression.
- Where progression is slowed, the user defines hazard ratios for affected transitions. For transitions unaffected by treatment, the hazard ratio defaults to 1. The user can include a period over which the effect of treatment wanes. During this period, the rate of progression returns to that of natural history in a linear fashion.
- Where the user defines an improvement in function or cure, a period of improvement is specified. At the end of this period, the redistribution of patients across health states is defined.
- The model includes both adverse and acute events defined by the user. Adverse events are associated with current treatment. Acute events are related to the sequelae of DMD, e.g. spinal surgery for scoliosis, or prior treatment, e.g. fracture resulting from prior OCS use.

Table 3: Defining treatment effects

	Period of				Reduction in adverse and/or acute events*
	Improvement	Stabilisation	Slowed progression	Waning effect	
Manage symptoms / reduce use of OCS					X
Slow progression			X	X	X
Halt progression		X	X	X	X
Regenerative therapies	X	X	X	X	X

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Conclusions

- The disease level cost-effectiveness model developed has provided a core model suitable for supporting HTA submissions for emerging and future treatments for DMD.
- The model provides a robust representation of the natural history of DMD, a common methodology and the flexibility required by the manufacturers to model their interventions, decision problems and modelling preferences.
- This case study illustrates the potential for collaboration between manufacturers in rare diseases to develop a single cost-effectiveness model which meets the needs of the different manufacturers without compromising confidentiality.
- Learnings from the case study suggest that collaborations and the development of template models may be beneficial in other rare diseases.

References

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