HERCULES, DUCHENE VITE IN LEADING E VIDENCE S VITES IS **PROJECT HERCULES: overcoming the Health Technology Assessment** hurdle through patient led collaboration

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The HTA hurdle for rare diseases

Drug development for rare diseases faces a number of hurdles to prove safety, efficacy and quality in order to achieve a marketing authorisation from regulators. In most European countries this is then followed by a fourth hurdle: Health Technology Assessment (HTA). HTA bodies typically assess the clinical and cost effectiveness of new treatments. looking for evidence beyond that required by regulators such as the EMA or FDA.

HTA bodies ask not just whether the new drug has a clinical benefit but the size of that benefit and the cost of the treatment to a health system. This can be particularly challenging for treatments for rare diseases.

The uncertainties inherent in assessing new treatments for rare diseases, particularly life-long progressive conditions, can make it difficult to ensure a successful HTA.

Project HERCULES was established by Duchenne UK in response to the absence of evidence for HTA for treatments for Duchenne Muscular Dystrophy (DMD) that fully reflected the experience of families and carers

What is Project HERCULES?

Project HERCULES is a collaborative international project set up and led by Duchenne UK, a patient organisation, to bring together pharmaceutical companies, academia, HTA bodies, clinicians, and patients to build tools and evidence at a disease level for use in HTA focused on Duchenne Muscular Dystrophy. These include four core workstreams:

- Natural History Model
- Quality of Life Metric
- Burden of Illness Study
- Economic Model



How does Project HERCULES work?

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DUCHENNE UK

Source

Project HERCULES is overseen by an international multi-stakeholder Steering Group including patient organisations, clinicians, health economists and other academics along with HTA agencies and sponsoring companies.

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The Project HERCULES core team ensure patients are at the centre of all workstreams with ongoing dialogue between the workstream leads and that the input of international patients, clinicians and other stakeholders informs all aspects of the work. This collaborative disease level approach represents an innovative approach to developing tools and evidence for HTA.

Each work stream has been driven by patient and clinical input and involved active collaboration with the Project HERCULES Steering Group which includes a range of stakeholders. This new paradigm for collaboration in HTA has brought many benefits along with some unexpected challenges. Here we explore the benefits and challenges in the natural history and quality of life workstreams.

Natural History Model

University of Leicester (UoL) are constructing the Natural History Model (NHM) working with The Duchenne Regulatory Science Consortium, at the Critical Path Institute. A Multi-State Model (MSM), consisting of health states and transitions between these states, has been fitted to the available data to describe the DMD disease pathway.

Project HERCULES has identified aspects of DMD not accurately reflected in published literature or the data routinely collected in clinical practice:

- Patients and families consistently identified the importance of being able to weight bear and support transfers. The loss of this ability often triggers the need for additional support such as hoists, adapted vehicles and home adaptations as well as impacting on clinical care and caregiver strain. Despite this, limited data was available for patients in this stage of DMD with some patients perhaps passing through this stage between clinic visits.
- Few available data sets included mortality data.
- Common Quality of Life metrics did not capture what was most important to people living with DMD.

This resulted in inclusion of the newly described transfer stage in the NHM despite the limitations of published data. This stage has been validated with patients and clinicians who recognise its importance for quality of life, clinical care and the financial burden of disease.



Quality of Life

A review of existing Patient Reported Outcomes (PROs) found that no measures were adequate to capture the complexity of DMD. The University of Sheffield are developing a Quality of Life measure for DMD that will map on to the health states defined in the Natural History Model and will be included in the Burden of Illness study. Initial patient views were represented by Duchenne UK, contributing to the research aims and design of the project. An established patient and public involvement group, including adults with DMD and parents of children with DMD contributed as research peers. This involvement identified priorities such as pain that were not well recognised by clinicians.

Stage 1	Systematic literature review of existing QoL instruments used for people with DMD Found no PBM - confirmed a need for a new QoL instrument to be developed
Stage 2	Qualitative interviews with people with DMD to find out what impacts on their life O domains identified, although some are not appropriate for inclusion in a QoL instrument
Stage 3	Developing and refining draft items to include in Stage 4 through cognitive debriefing Small sample (n=30, people with DMD, parents and clinicians)
	Psychometric survey (N=100-300 participants) using online or paper UK only sample (England) Analysis of survey data comparing with existing OpL instruments
Stage 4	Final item selection (informed with clinical input and people with DMD
Stage5	Obtaining utility weights for UK using DCE (online) with general population

Next steps

Project HERCULES outputs are tested with patients, parents and caregivers and at multi disciplinary advisory boards. All outputs will be published. Findings from Project HERCULES have revealed further evidence gaps to be filled, including:

- Clinical data on ability to weight bear
- Accurate mortality data
- · The impact of steroids
- Carer quality of life
- Global burden of disease

Project HERCULES will work to address the data gaps in collaboration with patients and clinicians. A core set of 10 translations for the DMD Quality of Life measure is also planned.

Conclusion

Patient communities are not simply the subject of research, they can direct research, ensuring the lived experience of a condition informs every aspect of health economics and outcomes research leading to results that better reflect the true impact of that condition and demonstrating value in treatments that can delay or halt progression. The leadership of a patient organisation ensures that Project HERCULES' focus is on the patient; enables access to data sources and expertise which may be inaccessible for individual researchers and ensures a bottom up approach to HTA evidence. This has led to the identification of a newly defined health state for DMD, the creation of a measure for Quality of Life in DMD that identified issues important to patients that were not well recognised by clinicians and a Burden of Illness study that identified those elements of DMD that have the biggest impact on patients and families. The Project HERCULES approach to patient engagement could provide a model for other rare disease communities.

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