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Chapter 6
Patient-Led Collaboration for HTA Tools and Evidence Development: Project HERCULES

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6.1 Introduction

This chapter describes the role of patients (in particular carers who are experts in patient advocacy) as leaders in Project HERCULES,[1] an international patient-led collaboration that has developed tools and evidence to support health technology assessment (HTA) for new treatments for Duchenne muscular dystrophy (DMD). This collaboration was initiated and is led by the patient community and has brought together patients and other experts (including clinicians, technology developer representatives, academics and HTA experts). The chapter explores when a patient-led collaboration for HTA may be appropriate and how the governance structure of Project HERCULES put patients at the heart of even the most technical work streams of the project. We look at the challenges in establishing Project HERCULES and the role of patients in the work on developing a validated measure for health-related quality of life (HRQoL), and in building a natural history model and disease-level economic model.

[1] HEalth Research Collaboration United in Leading Evidence Synthesis; https://www.duchenneuk.org/project-hercules/.

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6.2 The Case for Patient-Led Collaborations

HTA requires several disease-level inputs including a natural history model, HRQoL and cost of illness and various inputs to build economic models. In rare diseases there may be few clinical experts, little published evidence, and a limited pool of patients to provide this evidence. Building a robust evidence base can be expensive and time consuming, often prohibitively so for smaller biotech companies. Project HERCULES was established by Duchenne UK in response to the need for disease level tools and evidence to support HTA in DMD. The aim was to establish a patient-led collaboration to build a natural history model, economic model, HRQoL metric and build evidence on the burden and cost of DMD.

Project HERCULES is managed by Duchenne UK through a core team including those with lived experience of Duchenne as well as experience in HTA in rare diseases. Individual work streams are, where necessary, delivered by external vendors. An international multistakeholder Steering Group agrees the overarching work programme and members of this group advise on the work. Work is funded by Duchenne UK and pharmaceutical company members of the Project HERCULES Steering Group.

6.3 The Project HERCULES Approach

DMD is a serious genetic disease which is life-threatening and shortens the patient's life substantially. DMD is an X-linked disorder caused by mutations in the dystrophin gene and it is the most frequent muscular dystrophy in boys, affecting 1 in 3500 live births (Katirji et al. 2013; Mendell et al. 2013) and 1 in 50 million girls. DMD is usually diagnosed before the age of six. The disease causes progressive and unyielding muscle weakness frequently identified in the early toddler years when the child begins to miss development motor milestones (Henricson et al. 2013; Connolly et al. 2013). Loss of ambulation occurs generally around the age of 12. Only a few DMD patients survive beyond the third decade; most die because of respiratory complications or heart failure due to cardiomyopathy (Ricotti et al. 2019; van Ruiten et al. 2017; Bushby et al. 2010; Birnkrant et al. 2018).

Some HTA bodies struggled to reach decisions about the first licensed product for DMD, for example it was two and a half years after licence that the National Institute for Health and Care Excellence (NICE) guidance on the use of Ataluren in DMD was issued (National Institute for Health and Care Excellence 2016). The high cost of drug development, poorly documented natural history of the disease, lack of disease specific and age-appropriate endpoints that truly represent disease burden and the challenges of recruiting patients are major factors in hindering development, approval and reimbursement of new drugs for rare diseases (Nicod et al. 2019).

Duchenne UK was a stakeholder in a NICE appraisal of a treatment for DMD and witnessed a lengthy process which, in part, was due to gaps in the disease level evidence base. Duchenne UK recognised that determinations of value were based on limited evidence and models of cost effectiveness that did not fully characterise the experience of patients and carers with DMD (National Institute for Health and Care Excellence 2016). Duchenne UK proposed that for a rare disease with a limited patient population, non-competitive collaboration across all interested developers with relevant experts (patients, clinicians, academics, HTA) would be efficient and reduce the demand on patients and families who might otherwise be asked to participate in multiple, similar surveys or focus groups (Hatswell and Chandler 2017). Duchenne UK invited pharmaceutical companies with a DMD product in development to a training day in February 2017 to explore modelling and HTA in DMD. This led to a proposal from the patient organisation to establish Project HERCULES to drive development of a single disease-level economic model (rather than different companies developing models for their own products) and a core suite of associated tools to support the development of patient-focused evidence to input to HTA value determinations, including:

- A natural history model
- A bespoke HRQoL preference-based measure
- Burden of illness data.

Companies were invited to sponsor the work and join the Project HERCULES Steering Group together with international patient organisations, clinicians, academics and HTA experts. Full details of current Steering Group membership can be found at www.duchenneuk.org/project-hercules/project-hercules-team/.

All work was on the disease level rather than product specific, reducing the risk of conflict of interest or compliance issues for any of the stakeholders.

Project HERCULES is led by Duchenne UK with a core team of three, consisting of: the joint Chief Executive Officer of Duchenne UK (a parent of a son with DMD); a senior technology developer health economist (also a parent of a son with DMD); and an expert in HTA for rare diseases (previously an Associate Director at NICE, the UK's reimbursement decision maker).

This patient leadership set the priorities so that the outputs reflected individual and family experiences of people living with DMD, and enabled access to data sources and expertise which may be inaccessible for individual researchers.

Members of the Steering Group were proposed by the patient organisation and once established additional members were proposed by these Steering Group members. In rare diseases there are limited experts, and they are usually well known to others in the field, making establishing the Steering Group a relatively simple process.

Insights from patient organisations and people with lived experience of DMD were included in all Steering Group meetings and these directed the evolution of the work, having a major impact on the development of the evidence and tools. The initial work programme was proposed by Duchenne UK and agreed by the Steering Group. As work progressed it became evident that the broader impacts on patients and their families need to be captured and additional pieces of work were commissioned to explore specific aspects such as the impact of using steroids or the impact of the disease on familial carers.

Project HERCULES was designed to meet the needs of international HTA processes and quality requirements in a way that remained patient focused. Depending on their areas of expertise, steering group members contributed to the work streams, which were co-led with academics and researchers (Fig. 6.1). All outputs were reviewed by the Steering Group in addition to patient organisations and individual patients and parents.

Project HERCULES welcomed active participation from all stakeholders. Pharmaceutical companies sponsoring the work programme were full members of the Steering Group. As the primary end users (along with HTA bodies and payers) of the outputs of Project HERCULES, their contributions have been essential in ensuring the tools and evidence not only reflect the lived experience of patients and families, but also have a clear practical use for submissions to HTA. Technology developer involvement has been carefully managed to ensure full compliance with the ABPI Code of Practice for the Pharmaceutical Industry (ABPI 2021) and avoid any anti-competitiveness or conflicts of interest. Likewise, the HTA perspective was represented regularly by NICE and experts in HTA and health economics research.

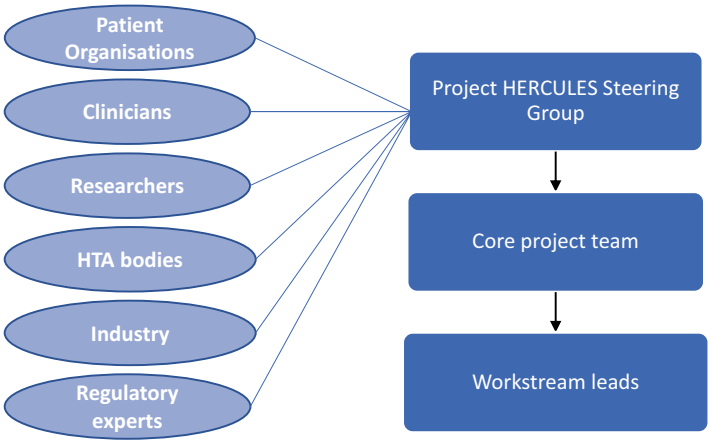

Fig. 6.1 Governance structure for project HERCULES

6.4 Targeted Methods for Patient Participation in Project HERCULES

As well as being patient led, via Duchenne UK, Project HERCULES incorporated active patient participation in all work streams. Duchenne UK recruited patients and parents to participate in the research through the use of social media and offline networks. This section outlines the different methods used to support effective participation in each work stream, which evolved as the research developed.

Economic models enable the assessment of the cost-effectiveness and impact on healthcare systems of new medicines, using clinical data, treatment costs, and health outcomes. They are typically developed by manufacturers for individual treatments to assess their cost-effectiveness and impact on healthcare systems once late stage clinical trials are underway. Economic models focus on health states that have a significant impact on clinical outcomes, HRQoL and/or healthcare resources and costs. The Project HERCULES economic model was constructed using the health states defined in the natural history model and burden of illness data. In an innovative step, the economic model was developed to be suitable for use in the assessment of any treatment for DMD, addressing cost effectiveness in multiple ways, and also to be used for treatments of specific symptoms as well as disease modifying treatments. It was validated by patients through advisory boards and Steering Group participation.

An iterative approach to developing the individual work streams meant that input from patients and informal carers could be used for multiple purposes, ensuring effective use of patients' and families' time.

6.4.1 Natural History Model

DMD has long been described along four health states: early ambulatory, late ambulatory, early non-ambulatory, and late non-ambulatory. These stages of progression are well-established in clinical guidelines on the diagnosis and management of DMD (Bushby et al. 2010; Birnkrant et al. 2018).

When Project HERCULES set out to build a natural history model for DMD, the patient leadership embedded lived experience in the project design and every stage of the model development, strengthening the input of patients and families to ensure that health states represented their lived experience and reflected a significant change in the clinical and/or financial burden of the disease.

The natural history model was built from a broad collection of clinical data in DMD in collaboration with the Duchenne Regulatory Science Consortium (D-RSC) (Conrado et al. 2019), part of the Critical Path Institute (2024). D-RSC is a non-profit consortium focused on regulatory science, which includes a US patient organisation, Parent Project Muscular Dystrophy and other individual patient/carer representation. Placebo data from completed clinical trials were also included. The Project HERCULES core team

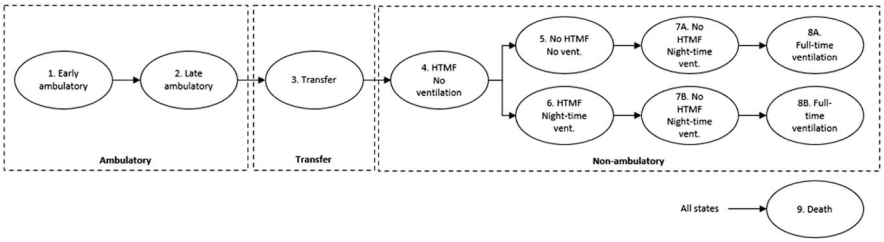

Fig. 6.2 Natural history model structure (Broomfield et al. 2024—http://creativecommons.org/licenses/by-nc/4.0/)

worked closely with the University of Leicester to ensure emerging findings were compared with real world experiences of patients and families through advisory board meetings and findings of the HRQoL work stream. Patient and clinical advisory groups reviewed data and provided input into definitions of health states.

Patient and family input was elicited at an initial advisory board meeting. During this meeting, it became clear that the standard distinction between late ambulatory and early non-ambulatory health states failed to adequately capture important aspects of DMD. Patients and relatives unanimously emphasised the importance of being able to weight bear and assist with transfers. They reported that the loss of this ability often triggers the need for additional support such as hoists, adapted vehicles and home adaptations, and can impact the carer (often the parent) financially, emotionally and physically. This input led to the inclusion of a transfer state between the late ambulatory and early non-ambulatory states in the natural history model, where patients can still weight bear but are no longer able to walk. This health state had previously been overlooked in data collection, natural history models and economic decision models.

Input from patients and families also identified more granular nuance in the non-ambulatory phase of DMD, including the loss of hand-to-mouth function alongside the introduction of night-time and thereafter full-time ventilation. The subsequent natural history model comprised nine main health states including death (see Fig. 6.2). Patient and family input was taken to confirm these health states for the natural history model at a second advisory board meeting (Broomfield et al. 2024).

These health states reflect states that have a significant impact on clinical outcomes, HRQoL, and/or healthcare resource use and the burden of illness. They informed the Project HERCULES HRQoL and burden of illness work streams, and the economic model (Woodcock et al. 2019).

6.4.2 Health-Related Quality of Life

Research into HRQoL was driven by both a recognised need within the Duchenne community to better measure quality of life in people with DMD and the known requirements from many HTA bodies for preference-based measures of HRQoL. The

objective was to develop a HRQoL patient-reported outcome measure (PROM) that is relevant to patients and allows estimation of utilities, an important measure for calculating quality-adjusted life years (QALYs). The QALY measure is an outcome measure that allows comparison of outcomes across multiple diseases and is the basis for cost utility analyses used by some HTA bodies. A systematic literature review, followed by application of COSMIN[2] methodology (Prinsen et al. 2018), demonstrated no suitable measure in DMD currently exists (Powell et al. 2020). Project HERCULES accepted the challenge to develop a new HRQoL preference-based measure in DMD. As well as being used to calculate QALYs, it was essential that the new PROM "measured what matters" to people living with Duchenne and that the patient voice was accurately represented (Powell et al. 2022). The measure was thus designed to have stronger content validity than any previous PROMs used in Duchenne. The novel measure became known as the DMD-QoL (Powell et al. 2021; Rowen et al. 2021).

Patient involvement was critical to the development of the DMD-QoL. At the outset, patient views were represented by Duchenne UK, contributing to the research aims and design of the project (i.e. to develop an outcome measure that captured what mattered to people living with DMD). The Project HERCULES core team worked closely with the University of Sheffield throughout this project, ensuring that each stage reflected lived experience, and jointly ran a patient and family advisory board to explore themes identified in patient interviews and surveys. A project-specific patient involvement group was established, which included adults with DMD and parents of children with DMD, who contributed throughout the project as research peers.

The development of the DMD-QoL consisted of three stages. In stage one, patient participation informed the design of semi structured interviews, including the areas of focus (see Supplementary File 1 of Powell and Carlton (2023) for topic guide) and appropriateness of topics for given age groups. Interviews were conducted with DMD patients and analysed to produce a draft framework for understanding HRQoL in DMD (Powell and Carlton 2023). This initial collaborative activity facilitated an active role for patient input into framing the research questions addressed during the patient interviews.

In the second stage, patients, clinicians and DMD carers assessed the face validity of the HRQoL framework, followed by a quantitative survey of a larger sample of patients, which was psychometrically analysed. At this stage, potential items for the DMD-QoL were ranked for their importance by patients and parents in an advisory group discussion using a traffic-light system facilitated by the research team (green = include in DMD-QoL, red = do not include in DMD-QoL, amber = uncertain, for discussion). Six people living with DMD and/or their carers contributed to this exercise, as well as five clinicians. The different perspectives employed in stage two informed the final item selection and highlighted differences in opinions between patients, families, and clinicians on proposed items for the questionnaire.

[2] COnsensus-based Standards for the selection of health Measurement INstruments.

It was considered important that the instrument would be equally useful for clinical, patient related, and HTA purposes. Therefore, it was important to gain input from all perspectives and then weight the different perspectives in a way that ensured the patient perspective had a priority without diminishing the usefulness to other stakeholders. In the development of the DMD-QoL patient views were always prioritised. In the third stage, an online discrete choice experiment was administered to a general public sample to weight the different elements identified and thus generate UK utility values (Rowen et al. 2021). Throughout the project, collaboration with people with DMD helped to construct the measure so as to meet the needs of people with DMD and their families (Powell et al. 2019).

6.4.3 Burden of Illness

Project HERCULES commissioned work looking at the burden of illness to explore the impacts of DMD that patients, families and clinicians identified as most important to them. The core team helped identify the items of most relevance for patients and HTA bodies to inform this work stream.

A UK burden of illness study was conducted. The study set out to provide health state costs for the economic model by applying unit costs to estimates of annual resource use for patients in each health state. The Project HERCULES Steering Group, which included a patient representative and two mothers of individuals with DMD, reviewed and approved the initial study outline.

A sample of 18 neuromuscular specialists completed an electronic case report form for the next 10 eligible patients they consulted. The specialists identified and extracted direct medical resource use information from the patients' Electronic Health Medical Records for the preceding 12-month period. The patients were then invited to complete a bespoke Patient Public Involvement Engagement (PPIE) questionnaire to capture data for direct non-medical resource use and work productivity impact. The survey was designed with survey responses from clinicians, patients and families and discussions at Project HERCULES Steering Group meetings (Evans et al. 2019). Dependent on the age of the patient, the questionnaire was completed by the patient (16 years or older), the patient's primary carer (4–7 years old), or a combination of both (8–16 years old).

The study found that overall indirect costs were the main driver of total cost in people with DMD, with the lost opportunity cost of work being the main driver for indirect costs. This key finding was only possible due to the involvement of patients and their families and the use of a PPIE questionnaire.

Key issues identified through this work informed the later detailed review of routine NHS data sets (Morgan et al. 2024) and work exploring patient, family and clinician views of the burden of steroids involving online surveys to inform themes explored in a small group, two dyad interviews with patients and their parents followed by a focus group with patients, carers and healthcare professionals.

6.4.4 Economic Model for DMD

The Project HERCULES economic model provides a robust core economic model suitable for submission to HTA bodies that is representative of the patients' and their families' progression through DMD. The model structure adopts a Markov approach which captures patients' HRQoL, health care resource use and cost, and mortality associated with progression of disease.

While the technical details of economic models are likely to be inaccessible to those without expert training in the area, the input of patients and their families shaped the structure of the model and its core data set. The model health states reflect those in the natural history model, which were defined with the input of patients and their families. The model was developed iteratively with patient and family involvement in its review at Steering Group meetings. In addition, the core data set for the economic model was developed with patient and family involvement in the burden of illness and HRQoL work streams.

This approach resulted in a development process led by patients, family and clinicians to complement findings from the published literature and clinical trials.

6.5 Challenges for Project HERCULES

The collaborative approach taken by Project HERCULES was not without challenges (Box 6.1).

Box 6.1 Challenges of the Collaborative Approach

- Demonstrating the capability of Duchenne UK to deliver an ambitious programme of health economics research
- Establishing the governance and financial arrangements for Project HERCULES with technology developer sponsors unused to working with patient organisations as leaders in health economics research
- Embedding lived experience in every aspect of Project HERCULES
- Ensuring involvement and engagement in a rare and complex health condition, including making appropriate and necessary adjustments for meetings, patient days, etc.
- Representation and diversity (i.e. not all parts of the patient community were represented and why that is difficult to do)
- Managing patient burden—an ambitious work programme requested multiple inputs from some patients and families.

Establishing Project HERCULES required significant investment by Duchenne UK to establish a work plan and bring sponsors and Steering Group members together, initiating some work prior to signing contracts.

There was some initial scepticism from technology developers and other partners who had concerns that a patient organisation would not bring the expertise, skills and experience necessary to deliver an effective programme of health economics research. Duchenne UK sought early involvement from experts and ensured that specialists in HTA, rare diseases and health economics were included in the project leadership team. Commissioning early research from the University of Sheffield into HRQoL also helped demonstrate to stakeholders the commitment and ability to deliver high quality outputs.

The governance and financial arrangements were complicated by the requirements around technology developer funding to patient organisations. Interpretations around the rules governing this varied by company, leading to extensive negotiations with most sponsors, made more challenging by the need to ensure consistency across contracts. Ultimately all issues were resolved but the lengthy discussions led to inevitable delays in funding. Duchenne UK approached these discussions offering as much flexibility as possible to each company, within the framework of the overarching approach to Project HERCULES and the need to ensure no individual company received preferential terms.

Researchers often needed to learn to explain complex concepts in accessible language to a non-expert audience so that patients and families could contribute effectively. This included researchers learning to explain what aspects of a disease are important to HTA processes, the specific requirements as to how those aspects should be measured and some of the more technical elements of the project such as the economic model. Balancing input from patients and families with clinical, technology developer and HTA experts has also been challenging. Project HERCULES selected researchers in part by their readiness to work collaboratively with patients, families and other stakeholders by actively listening and responding to all the information received not simply seeking confirmation of what they expected to find.

Throughout Project HERCULES attention was given to minimising the burden on patients and families of participation in research. This included careful consideration of the amount of patient participation in individual work streams and the most appropriate methods for achieving this participation. Rare disease patients may find themselves burdened by repeated requests for information and a key aim of Project HERCULES was to avoid duplication and unnecessary information gathering wherever possible.

Minimising the burden on patients included ensuring patients and families were able to participate in the research at a time and location that would fit around their logistical requirements such as work, caring responsibilities or access requirements.

Ensuring a representative sample of patients and families was and remains challenging. We were aware that certain demographics are more likely to respond to surveys, requests for interviews and focus groups and despite efforts to address this,

the sample of patients was not fully representative of the whole population. More work is needed to ensure diversity of representation in health economics research, for example mothers were over represented in our engagement with families and the geographical, economic and ethnic diversity of those engaging in the programme could be improved.

Despite the challenges, Project HERCULES has consistently taken a patient-led approach that has had a clear impact on each work stream (Box 6.2).

Box 6.2 Impacts of a Patient-Led Approach

- Identifying the need for the research, scoping its work streams and creating an inclusive way of working for a wide range of stakeholders
- Enabling researchers to test assumptions against lived experience and develop their own understanding of the condition and care pathway
- Identification of meaningful disease stages including the previously overlooked state between the traditional stages of late ambulatory and early non ambulatory, reflecting patient and parent experiences of the importance of being able to weight bear
- Development of a bespoke HRQoL preference-based measure that better reflects the lived experiences of those with DMD as well as the views of clinicians and other experts
- An economic model that builds on the actual experience of patients and families and has been well received by HTA professionals
- A burden of illness study focusing on what is most important to patients and families
- The identification of future priorities that reflect what is most important to patients and families, including the impact of long-term high dose steroid use and the burden and quality of life of parents and family carers.

6.6 Discussion

Project HERCULES has demonstrated that patient communities can direct health economics research, working as peers with academics, clinicians, HTA experts and other stakeholders to ensure that the disease-level evidence used in HTA decisions reflects the lived experience of patients and families. Indeed, patient-led health economics research can improve the relevance of health economics research outputs. The evidence and tools are available to companies developing treatments for DMD, raising the quality of the evidence and its presentation to HTA, shortening time to patient access, saving the costs of duplication of effort by multiple companies, and making efficient use of a small patient pool.

Challenges in patient involvement in health economics research can be overcome and patient-led collaborations can help ensure that this is a priority for research, avoiding marginalisation of patients' contributions.

Duchenne UK embarked on an ambitious programme and made substantial financial and staff investments into this which were essential to ensuring its success, along with other key factors (Box 6.3).

Box 6.3 Key Success Factors

- Ensuring patients and families were leading the work as well as participating in the work
- Embedding subject matter expertise alongside lived experience in the project leadership
- Iterative and responsive communications with all stakeholders including regular updates for patients and families to explain the aims of Project HERCULES, progress being made, and the impact patient contributions made to this work
- Identifying and collaborating in all work streams with qualified research experts, who were willing to adapt their work processes to the required focus on patient needs and patient leadership
- A project management team that ensured work stream leads were committed to capturing patient and family perspectives, providing feedback on how the input had been used, and to working collaboratively where possible to ensure learnings from each work stream informed the other work streams.

The Project HERCULES approach could be used in other disease areas. Indeed, it has informed the development of collaborative programmes for HTA in other rare diseases, including Project Mercury for facioscapulohumeral muscular dystrophy (FSHD).

Collaboration with patients and families can completely change the perception of researchers, providing insights that allow evidence to be understood differently and directly affecting the outputs of each work stream.

Bringing stakeholders together in a non-competitive space can have many benefits for all stakeholders preparing for HTA in rare diseases (Box 6.4).

Box 6.4 Benefits for Stakeholders

- Access to a wider pool of expertise and evidence, maximising the impact of patient data and insights and ensuring that evidence reflects patients' and families' experiences
- Minimising the demands placed on patients, families, and clinicians to repeatedly share their evidence and insights to inform individual pharmaceutical company work programmes (particularly relevant in areas such as DMD which has a number of treatments in development)

(continued)

Box 6.4 (continued)

- Better quality tools and evidence to inform HTA decisions, developed independently from any single life sciences company
- Spreading financial burden across multiple organisations
- Developing disease level tools and evidence well in advance of HTA requirements, enabling them to be shared with HTA bodies and allowing a consistent approach to evaluating new treatments
- Avoiding duplication of effort across different stakeholder groups.

Patient organisations are well placed to lead these collaborations as experts in the impact of the condition(s) they represent. A patient organisation-led approach to building tools and evidence for HTA, in collaboration with qualified researchers and other stakeholders, can effectively ensure that the lived experience of a condition informs every aspect of health economics and outcomes research, leading to results that better reflect the impact of that condition, or a new health technology, on patients' lives. Such evidence can help in demonstrating value of new therapies in a patient relevant way.

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References

ABPI. Code of practice for the pharmaceutical industry 2021. ABPI. 2021. https://www.abpi.org.uk/publications/code-of-practice-for-the-pharmaceutical-industry-2021/. Accessed 7 Oct 2024.

Birnkrant DJ, Bushby K, Bann CM, Apkon SD, Blackwell A, Brumbaugh D, et al. Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and neuromuscular, rehabilitation, endocrine, and gastrointestinal and nutritional management. Lancet Neurol. 2018;17:251–67. https://doi.org/10.1016/S1474-4422(18)30024-3.

Broomfield J, Hill M, Chandler F, et al. Developing a natural history model for Duchenne muscular dystrophy. PharmacoEconomics Open. 2024;8:79–89. https://doi.org/10.1007/s41669-023-00450-x.

Bushby K, Finkel R, Birnkrant DJ, Case LE, Clemens PR, Cripe L, et al. Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and pharmacological and psychosocial management. Lancet Neurol. 2010;9:77–93. https://doi.org/10.1016/S1474-4422(09)70271-6.

Connolly AM, Florence JM, Cradock MM, Malkus EC, Schierbecker JR, Siener CA, et al. Motor and cognitive assessment of infants and young boys with Duchenne muscular dystrophy: results from the Muscular Dystrophy Association DMD clinical research network. Neuromuscul Disord. 2013;23:529–39. https://doi.org/10.1016/j.nmd.2013.04.005.

Conrado DJ, Larkindale J, Berg A, Hill M, Burton J, Abrams KR, et al. Towards regulatory endorsement of drug development tools to promote the application of model-informed drug development in Duchenne muscular dystrophy. J Pharmacokinet Pharmacodyn. 2019;46:441–55. https://doi.org/10.1007/s10928-019-09642-7.

Critical Path Institute. The path forward in drug development. https://c-path.org/. Accessed 7 Oct 2024.

Evans J, Rose A, Martin A, O'Hara J, Chandler F, Godfrey J. Project HERCULES – a modified Delphi survey to inform a burden of illness study in Duchenne muscular dystrophy. Value Health. 2019;22:S870. https://doi.org/10.1016/j.jval.2019.09.2480.

Hatswell AJ, Chandler F. Sharing is caring: the case for company-level collaboration in pharmacoeconomic modelling. PharmacoEconomics. 2017;35:755–7. https://doi.org/10.1007/s40273-017-0516-2.

Henricson EK, Abresch RT, Cnaan A, Hu F, Duong T, Arrieta A, et al. The cooperative international neuromuscular research group Duchenne natural history study: glucocorticoid treatment preserves clinically meaningful functional milestones and reduces rate of disease progression as measured by manual muscle testing and other commonly used clinical trial outcome measures: CINRG DMD natural history study. Muscle Nerve. 2013;48:55–67. https://doi.org/10.1002/mus.23808.

Katirji B, Kaminski HJ, Ruff R, editors. Neuromuscular disorders in clinical practice. 2nd ed. New York, NY: Springer; 2013. https://doi.org/10.1007/978-1-4614-6567-6.

Mendell JR, Rodino-Klapac LR, Sahenk Z, Roush K, Bird L, Lowes LP, et al. Eteplirsen for the treatment of Duchenne muscular dystrophy. Ann Neurol. 2013;74:637–47. https://doi.org/10.1002/ana.23982.

Morgan CL, Godfrey J, Chandler F, et al. Epidemiology and healthcare resource utilisation associated with Duchenne muscular dystrophy. J Rare Dis. 2024;3:23. https://doi.org/10.1007/s44162-024-00044-z.

National Institute for Health and Care Excellence. Ataluren for treating Duchenne muscular dystrophy with a nonsense mutation in the dystrophin gene. In: Guidance. NICE. 2016. https://www.nice.org.uk/guidance/hst3. Accessed 7 Oct 2024.

Nicod E, Annemans L, Bucsics A, Lee A, Upadhyaya S, Facey K. HTA programme response to the challenges of dealing with orphan medical products: process evaluation in selected European countries. Health Policy. 2019;123:140–51. https://doi.org/10.1016/j.healthpol.2017.03.009.

Parent Project Muscular Dystrophy. Parent Project Muscular Dystrophy. https://www.parentprojectmd.org/. Accessed 7 Oct 2024.

Powell PA, Carlton J, Rowen D, Brazier JE. Producing a preference-based quality of life measure for people with Duchenne muscular dystrophy: a mixed-methods study protocol. BMJ Open. 2019;9:e023685. https://doi.org/10.1136/bmjopen-2018-023685.

Powell PA, Carlton J, Woods HB, Mazzone P. Measuring quality of life in Duchenne muscular dystrophy: a systematic review of the content and structural validity of commonly used instruments. Health Qual Life Outcomes. 2020;18:263. https://doi.org/10.1186/s12955-020-01511-z.

Powell PA, Carlton J, Rowen D, Chandler F, Guglieri M, Brazier JE. Development of a new quality of life measure for Duchenne muscular dystrophy using mixed methods: the DMD-QoL: the DMD-QoL. Neurology. 2021;96:e2438–50. https://doi.org/10.1212/WNL.0000000000011896.

Powell PA, Carlton J, Rowen D, Brazier J, Facey K, Bayley K, et al. Measuring what matters: little evidence supporting the content validity of EQ-5D in people with Duchenne muscu-

lar dystrophy and their caregivers. Med Decis Mak. 2022;42:139–40. https://doi.org/10.1177/0272989X211062237.

Powell PA, Carlton J. A comprehensive qualitative framework for health-related quality of life in Duchenne muscular dystrophy. Qual Life Res. 2023;32:225–36. https://doi.org/10.1007/s11136-022-03240-w.

Prinsen CA, Mokkink LB, Bouter LM, Alonso J, Patrick DL, De Vet HC, Terwee CB. COSMIN guideline for systematic reviews of patient-reported outcome measures. Qual Life Res. 2018;27:1147–57. https://doi.org/10.1007/s11136-018-1798-3.

Ricotti V, Selby V, Ridout D, Domingos J, Decostre V, Mayhew A, et al. Respiratory and upper limb function as outcome measures in ambulant and non-ambulant subjects with Duchenne muscular dystrophy: a prospective multicentre study. Neuromuscul Disord. 2019;29:261–8. https://doi.org/10.1016/j.nmd.2019.02.002.

Rowen D, Powell P, Mukuria C, Carlton J, Norman R, Brazier J. Deriving a preference-based measure for people with Duchenne muscular dystrophy from the DMD-QoL. Value Health. 2021;24:1499–510. https://doi.org/10.1016/j.jval.2021.03.007.

van Ruiten H, Bushby K, Guglieri M. State-of-the-art advances in Duchenne muscular dystrophy. Eur Med J (Chelmsf). 2017;2:90–9. https://doi.org/10.33590/emj/10311993.

Woodcock F, Mumby-Croft J, Ghosh S, et al. Project HERCULES – a case study in developing a multi-company, flexible cost-effectiveness model in a rare disease. Value Health. 2019;22:S843. https://doi.org/10.1016/j.jval.2019.09.2347.