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Chapter

The Impact of Payer and Reimbursement Authorities Evidence Requirements on Healthcare Solution Design for Muscular Dystrophies

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Abstract

For rare diseases that start early and are slowly degenerative, despite the desire to create solutions that benefit the patient, healthcare system realities can be prohibitive to generate an affordable and effective solution. The optimal care pathway for muscular dystrophy, similar to all degenerative diseases, would be a rapid and accurate diagnosis, pathophysiological confirmation and application of therapeutics that slowly replaces damaged tissue with healthy tissue, supported by adjuvant solutions that stimulate the tissue to repair and reduce inflammation and fibrosis. This would increase the lifespan and quality of life in an affordable way. For all diseases, two key stakeholders, the paying entity and the patient, fundamentally define whether revenue can be generated. Healthcare decision-making commissioners who agree to pay for the product and patient-reported outcomes jointly inform whether the intervention increases the quality of life related to existing standards of care and, therefore, if it should be paid for. This chapter explains why this has not yet happened and efforts initiated to correct this and addresses how the components and data used in this decision-making process could be updated, adapted and integrated into every stage of the development of solutions and how organisational innovation may enable the field.

Keywords: HTA, PRO, evidence generation, innovation valuation, healthcare solution development

1. Introduction

Only around 5% of the 7000 identified rare diseases have an effective treatment and this is echoed in neuromuscular conditions [1]. Recent years have witnessed a number of cancelled developments of therapeutic interventions for muscular dystrophies that were at advanced stages of development, while other interventions

have been denied market authorisation, both in the US and Europe due to a lack of clinical efficacy. This means it is even more important to convince payers of the value for money of the few treatments that make it to market.

Obtaining market authorisation does not guarantee that payers will reimburse the product, that is pay for it, as growing concerns regarding the growing gap between the demand for health services and technologies and the available resources have increasingly introduced systems to assess the value for money of those products coming to market. The predominant processes for these value assessments are called health technology assessments (HTAs). Since the introduction of the National Institute for Health and Care Excellence (NICE) in 1999 in England, HTAs have spread throughout the world and now nearly every country has HTA organisations in place to help payers determine the value for money of new healthcare technologies.

These value assessments conducted by these HTA organisations consist of compiling, analysing, assessing and appraising the evidence available to show whether the health and economic benefits of a product compared to the standard of care (in the jurisdiction in question) are sufficient to justify the price, above and beyond the requirements of regulatory authorities.

There remains a lack of understanding and implementation of these considerations in clinical development without which companies will struggle to gain reimbursement.

Negative reimbursement decisions by payers hinder access to the drug substantially, if not completely. Delays in reimbursement decision-making can lead to substantial delays in a new product gaining market access. Both delays and negative decisions impact adversely on sales and consequently return of investment (ROI). Furthermore, where the evidence presented to reimbursement decision-makers bears too much uncertainty it is highly likely that the accepted price will be far below the one required by the manufacturer. Thus, investing in better data collection can support reimbursement at an acceptable price.

Given the central role played by clinical trials in generating the evidence required for HTAs, everyone involved in designing clinical trial programmes and evidence generation needs to be aware of the methods and procedures required to generate the evidence required for HTAs above and beyond the evidence requirements for regulatory approval.

This is critical for developing solutions for rare diseases, such as the muscular dystrophies, due, fundamentally, to the low number of patients, and the significant variation of disease progression and severity among the patients that makes the generation of authority stipulated convincing statistical evidence significantly more complicated [2]. There are still many treatments in late stages of clinical validation (phase II and III) and more in earlier stages of development [3] targeting as many different aspects of this multi-faceted disease as possible.

In this chapter, we present a framework for what to consider during the design of clinical trials and evidence generation alongside and beyond clinical trials for muscular dystrophies to address the evidence requirements to gain reimbursement by payers.

Concerns regarding the growing gap between demand for health services and technologies and available resources have long created the need to regulate healthcare expenditure and governments have increasingly introduced formal systems to assess the value or money of healthcare technologies coming to market [4]. Nearly every country has formal reimbursement authorities in place to help payers determine whether a health technology is worth paying for. Value assessments conducted by these authorities consist of compiling and analysing the evidence to show the health and economic benefits of a product compared to the standard of care are sufficient to justify the price desired beyond the requirements of the regulatory authorities [4].

Delays in reimbursement decision-making can lead to substantial delays in a new product gaining market access and negative reimbursement decisions by payers hinder market access substantially and thus impact adversely on sales and return on investment. Furthermore, where the evidence presented to reimbursement decision-makers bears too much uncertainty it is highly likely that the accepted price will be far below the one desired by the company. Thus, investing in better data can support reimbursement at a desired price.

Given the central role played by clinical trials in generating evidence for use in reimbursement assessments, those involved in designing clinical trials need to be aware of the evidence requirements of payers and reimbursement authorities. These differ and go beyond those of regulatory authorities.

We also explore the specifics of these issues and suggest actions that can be taken from conceptual design throughout the development of interventions that can help manufacturers unlock market access for their products. While all of the above applies to all pharmaceuticals, it is even more important in the context of muscular dystrophies and other rare disorders where data can only be generated in a small number of people as compared to more common conditions such as type 2 diabetes.

2. The patient care pathway and standard of care for the muscular dystrophies

From either a patient care and management procedure or a healthcare solution development perspective, in an ideal scenario three components are needed:

- An established and clearly defined pathophysiological assessment of the development of the disease that enables an accurate prognosis at any time point in the disease progression that a standardised diagnosis confirms;

- An overlapping and reimbursement agency-approved care pathway that defines what needs to be done at every point throughout the disease; and

- A list of the standards of care that are purchased and used throughout the care pathway.

These three components can be further complemented by population health dynamics that also integrates environmental and socio-economic components linked to patient groups that further refine best approaches.

For highly prevalent diseases, the large number of patients that are affected generates a large source of data from which statistically relevant conclusions can be drawn that inform the points above enabling healthcare practitioners to make optimised patient care decisions, while innovators can look at the pathway to identify 'pain points' for which a specific product can be created to generate a solution. For conditions such as many forms of cancer or cardiovascular diseases, this has been further augmented as global patient data collections have become integrated, thereby generating even more specific and highly tailored approaches.

Rare diseases do not and have never had the same broad evidence base as the highly prevalent diseases and that has been recognised by the key stakeholders including regulatory authorities and governments who have introduced incentives to encourage the development of new treatments for rare diseases. These stakeholders have globally networked and generated information and data resources such as the global academic network Treat NMD group (https://treat-nmd.org) focusing on all neuromuscular diseases to create a critical mass, ecosystem and hub of expertise.

Duchenne muscular dystrophy 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 [5, 6] and 1 in 50 million girls [7]. DMD is usually diagnosed before the age of 6. The disease causes progressive and unyielding muscle weakness frequently identified in the early toddler years when the child begins to miss development motor milestones [8, 9]. 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 [10–13].

From a clinical care perspective in DMD, because clinical care recommendations did not previously exist, the US Center for Disease control (CDC) established the DMD Care Considerations Working Group, who in 2010 published the first comprehensive DMD care considerations [12]. These were revisited and updated in 2018 to provide a complete care programme that addressed 11 key topics that occur in DMD, divided into five stages of disease [13–15]. The five recognised stages are diagnosis, early ambulatory, late ambulatory, early non-ambulatory and late non-ambulatory, and the 11 key topics include neuromuscular, rehabilitative, endocrine, gastrointestinal/nutritional, respiratory, cardiac, bone health, orthopaedic, psychosocial and transitions management. Within these publications the precise list of tests and actions that should be performed for these 11 topics at each stage are indicated. These initiatives have generated enormous amounts of benefit as proven by increased lifespans of patients and, critically, a drive to obtain even more detail about all the different characteristics of the disease and its precise progression [12, 16–19]. This has included a push to reintroduce newborn screening tools and a larger effort to understand the pathology at the earliest times of the disease, which has recently been approved by the FDA [20].

The widely held and logical argument is that the sooner the intervention is started, typically in the young child, the greater the possibility that quality of life, morbidity and length of life can be enhanced.

As the prelude to this chapter, we have analysed the approved patient care and management pathways and integrated more recent published reports on early stage assessments and longitudinal monitoring, incorporated in as much insight as possible from the most current knowledge to create a best 'what we know' about the progression of muscular dystrophies, with a bias towards Duchenne muscular dystrophy (DMD). This has been done on the basis that by analysing one muscular disease as comprehensively as possible it will complement insights from our peers for the additional muscular dystrophies.

All muscular dystrophies are genetic; DMD is X-linked and can be an inherited mutation, a spontaneous mutation or due to germline mosaicism. The onset of DMD is illustrated by a list of manifestations that serve as 'possible indicators' of the disease that then precipitates a diagnostic assessment pathway that confirms or refutes the evaluation [13].

As demonstrated in the Norwegian paediatric DMD population, if there is a family history of muscular dystrophy, then this can mean that a confirmed diagnosis is possible almost immediately (mean age at diagnosis 2.8 years with a standard deviation of 3.2 years) [21] if there is not; then indicators such as speech delay, high Creatinine Kinase or transaminases, abnormal gait or delayed motor development followed by more specific genetic tests are used to confirm diagnosis that may not occur until the child is between 3 and 6 years of age. Newborn screening for high CK is a good predictor of DMD.

Why is this important? Until recently, understanding of muscular dystrophy during the neonate phase was very limited and it was speculated that there was

a 'honeymoon period' during which the disease did not develop significantly. Following the creation of the Bayley III child development assessment tool, the MDA-DMD clinical research assessed 24 children with ages ranging from 0.37 months to 2.99 years [9]. The Bayley III tool assesses children in five developmental domains: cognition, language, social–emotional, motor and adaptive behaviour. It exists in tailored forms for specific diseases. For all patients, their language and cognitive skills were lower than healthy patients, as were their fine motor skills, while the gross motor skills were more significantly impacted, implying that the large muscle groups and the core muscle groups are being affected in these patients at an early age, and it was observed that these skills declined with age. In a 1-year follow-up, declining motor function continued to be observed [22]. This work was further confirmed in a larger study involving 114 patients in which delays in gross motor development were observed [23]. Similarly in the 4D-DMD study performed comparing the healthcare records and questionnaires of 76 patients with DMD compared to 19,000 patients from the general population revealed impaired gross motor development, with first signs visible at 2–3 months of age and more evident by 24 months of age [24].

Additionally there is early fibrosis in the newborn, and the possibility there may be a cardiac involvement without overt clinical signs [25], whether there are endocrinological or respiratory issues early in development is still unclear [26]. Given the gross motor involvement, it is possible that the diaphragm maybe affected, but no respiratory analyses in very young children have been reported. The diaphragm and abdominal muscles work in tandem to stabilise the spine and trunk and enable voluntary limb movement [27].

The standard of care is to start steroid treatment and physiotherapy from the age of 3 or 4, cardiac monitoring and spirometry, measuring pulmonary function and vital capacity, from the age of 6 [13–15] and it is known that from the age of 6 onwards there is respiratory decline peaking at around 14 years of age, with a forced vital capacity (FVC) of 1 L [28] while a healthy child typically has a FVC of over 3 L. Those patients with a strong FVC have been reported to live longer [29], so we can speculate based on the outcomes from the Bayley III analysis if respiratory assessment or diaphragm thickness analysis may also be worthwhile measures at early stages of disease that can be assessed more frequently in the family practice setting, providing the equipment is available and correctly maintained [30].

How to approach this from a rehabilitative approach, especially in the neonate, given their developmental and overall regenerative capacity could be avenues to explore experimentally in animal models. It is recommended that excessive and high-impact exercise should be avoided in these patients due to the induction of muscle damage, without the normal muscle repair mechanism, thereby augmenting inflammation and fibrosis [31]. However if there is specific muscle involvement enabling a localised application of regenerative approaches combined with occupational therapy or low-intensity rehabilitation, this may provide a foundation to prevent core muscle decline, and enable other therapies to be sequentially applied. Experimentally, this has been demonstrated in traumatic muscle damage [32, 33], while in Sarcopenia low-intensity electrical stimulation has demonstrated benefits [34, 35]. Whether these approaches can be innovated and combined, while addressing the genetic aspect is an open question; however, as shown for traumatic spinal cord injuries, combination approaches can offer benefit [36].

What happens next, generally to the patient is well documented and increasingly being reported linked to the type of mutation that the patient has (nonsense, frameshift, splicing site, pseudoexon or missense). Using North Star Ambulatory Assessment (NSAA) as the outcome assessment, mild increases are observed in functionality very early and then from the age of 3 to 6.5 years the patient's

ambulatory capacity increases [16] but it never reaches the age standardised healthy norm. Physical support maybe needed from the age of 8, and between the ages of 10 and 12 most patients no longer have the ability to walk, which also leads to orthopaedic-related issues (contractures in the ankles and scoliosis in 90% of patients) with associated impacts on cardiovascular and pulmonary function.

It is important to look at the specifics of each patient because of the patient variability (genetic type and likely population health-related compounding factors) and the 11 topics that are considered essential in patient care and management, as demonstrated by the studies of Phillips and Brogna [29, 37]. Despite mean assessments based upon Spirometry or 6MWT that indicate downward decline, at the individual patient level while eventually each patient's condition deteriorates, the variation between the genetic mutation (whether it is an early or late deletion, a duplication or premature stop codon) related to functionality or lung capacity indicates that there are additional compounding factors that influence pathology progression.

One trend does seem to be clear and that is when a patient's condition does deteriorate, it happens rapidly, in less than 12 months. This would suggest that a higher frequency of testing may be needed, which would for most families present a logistical problem. Therefore, patient management solutions that can be implemented either virtually as that performed in standard cardiac monitoring or in family care practices may offer innovative interim patient care and management alternatives.

Considering that every patient is typically monitored via a dedicated specialist centre, who without question perform as many of the recommended tests as possible, because no correlation has been reported between disease progression at the biometrics being assessed, there may be external factors influencing disease progression. This is not a strange phenomenon, in the instance of asthma, increased incidences of asthma are reported in lower income families, because in many cases the houses can be either mouldy or damp resulting in spores entering the child's lungs and inducing the disease [38]. It may therefore be worthwhile to integrate Population Health specialists into the ecosystem to provide additional insights, which may not generate an intervention, but will define an optimised and implementable care pathway that integrates for as many patient-specific non-disease specific variables as possible that can include broad social, socio-economic, environmental conditions as well as healthcare policies.

The cumulative outcome will hopefully be not only a globally standardised care pathway for all patients with muscular dystrophy, but also the creation of intervention and diagnostic innovations that will address reimbursement agencies' requirements and standards.

3. The evolution of reimbursement decision-making

Concerns regarding the growing gap between demand for health services and technologies and available resources have long created the need to regulate healthcare expenditure and governments have increasingly introduced formal systems to assess the value for money of healthcare technologies coming to market [4]. The predominant processes to do so are health technology assessments (HTAs) (ref).

The introduction of the National Institute for Health and Care Excellence (NICE) in 1999 in England significantly contributed to the globalisation of HTAs [39]. Nearly every country now has an HTA organisation in place to help payers determine the value of new medical interventions (**Figure 1**) [40].



Figure 1.
Countries with formal HTA systems worldwide.

Historically, HTAs were performed after regulatory marketing authorisation had been granted. Due to the resulting gap between marketing authorisation and reimbursement, HTAs tend now to start much earlier—often in parallel with regulatory approval processes.

While there are differences between countries regarding defining the value of a new health technology, certain central requirements are common and can be addressed in clinical trials and evidence generation alongside and beyond clinical trials.

HTA is constantly evolving—the methods and processes as well the countries using it. Therefore, manufacturers developing healthcare technologies need to follow and engage with HTA developments either directly or through the use of expert consultants.

4. HTA vs regulatory requirements

Regulatory authorities around the world require manufacturers to demonstrate the risks vs. benefits and quality based on clinical and non-clinical information. Reimbursement authorities require companies to demonstrate the comparative value of their product vs. the standard of care used in their jurisdiction. To do this, they appraise a new health technology or indication in comparing a set of product attributes relating to its efficacy, safety, impact on quality of life (QoL) and functional status and pricing compared to the current standard of care.

Evidence used in HTAs for assessing the relative clinical and cost-effectiveness of new pharmaceuticals comes from a variety of sources, such as systematic literature reviews, indirect treatment comparisons and economic modelling. However, clinical trials conducted during the drug development process provide the most important source of treatment effect data for HTAs.

In recent years, some regulators including the EMA and FDA have taken steps to enable faster access to some drugs for rare conditions. For example, grant conditional authorisation to treatments such as Ataluren for DMD. This is not without controversy and HTA authorities have expressed concern that there may be insufficient evidence available for them to determine the effectiveness and value of such treatments.

5. Common HTA data needs

Traditionally, most medicines received marketing authorisation after completion of large phase III clinical trials. Increasingly, medicines, especially such with novel or breakthrough status, are receiving regulatory approval based on much smaller phase II trials and/or non-comparative 'single arm' trials.

Therefore, it is important to consider the specific evidence requirements for HTAs (i.e. core of relative clinical and cost-effectiveness evidence) much earlier in clinical development programmes, that is, when designing phase II trials as well as when designing phase III trials.

Pharmaceutical companies need to consider five critical areas when designing clinical trials to be HTA ready as well as ready for regulatory authorities:

i. Choice of comparator

ii. Measurement of clinical effectiveness

iii. Quality of life (QoL) and patient reported outcomes

iv. The collection of resource use data

v. Follow-up time of the trial

5.1 Choice of comparator

Non-comparative/single arm trials create issues when HTA decision-makers try to compare the new technology vs. the standard of care. Placebo-controlled trials result in similar issues, if the placebo arm of the trial differs substantially from clinical practice. Both result in the need of extensive indirect treatment comparisons (ITCs), thus weakening the relevance and robustness of the clinical evidence in HTAs.

We recommend, wherever possible, to use the standard of care as the comparator. This may be difficult where there is no gold standard and/or where clinical practice across and/or within countries involved in the trial varies. In such cases, we recommend consideration of the use of an active comparator based on physician choice to enable treatment comparisons relevant to HTA decision-makers in their respective jurisdictions.

5.2 Measurement of clinical effectiveness (efficacy and safety)

HTA requires outcomes to be patient relevant, and there is a growing interest in the use of patient reported outcome measures (PROMs) in clinical trials [41–43]. In some disease areas, for example cancer, it may not be possible to power a trial to capture the treatment effect on hard outcomes, such as mortality/overall survival, and surrogate endpoints are used, such as progression free survival, which is an issue for ensuring the trial results are relevant to patient outcomes. However, surrogate endpoints can be useful when a clear and robust link can be established with patient relevant outcomes. For example, as for the link between HbA1c in type 2 diabetes and cardiovascular events. However, this is only when those links have been or can be validated by studies, so that HTA decision-makers can accept them.

We recommend, where possible, to select endpoints relevant to patient outcomes (for example survival, PROMs—see more below). Where this is not possible,

we recommend establishing robust links between surrogate endpoints and patient outcomes and to validate them in separate studies or with external databases.

When considering the selection of endpoints for a clinical trial, it is also important to keep in mind how the data will be used in HTAs where the new technology will be compared with other technologies used in clinical practice via an ITC. Therefore, it is important to review which endpoints have been collected in trials of most relevant comparator technologies to enable such treatment comparisons.

We recommend reviewing the endpoints used in previous trials, undertaking validation of these measures, whether the MCID is relevant and a predictor of patient outcomes and making a recommendation for consistent measures going forward to support comparisons between treatments.

However, there is non-alignment between the entities that provide market authorisation and those that perform HTAs. The FDA strongly recommends placebo-controlled trials [44], whereas the EMA suggests placebo in a two-way design study that enables a standard of care add on. With the caveat that if patients are being treated with corticosteroids, further patient stratification between the groups should be performed [45]. In both cases, a restoration of function or slowing decline is considered the main recommended endpoint, along with additional studies addressing activity levels, cardiac function and respiratory activity, while patient reported outcomes are suggested but not recommended.

Similarly, NICE in their evaluation of Idebenone, indicated that outcome measures to be considered could include pulmonary function, cardiac function, walking ability, motor function, muscle strength and HR-QOL, to assess the impact on quality of life [46].

This, however, is not reflected in the analysis of phase II and III clinical trials either performed or ongoing for muscular dystrophies. Of the 19 drugs tested in numerous phase III studies only 6 included PRO to enable a HR-QOL assessment, while of the 18 in phase II studies only 2 included PRO. One has to anticipate that because of the low number of patients in rare disease clinical trials and the importance of the impact of obtaining quality of life information to enable patients to have access to these medicines, PRO should become a standard in clinical studies, and that the PRO should be standardised throughout the field.

5.3 Quality of life (QoL) and patient reported outcomes (PROs)

HTA organisations use QoL and functional status data either for use in cost-effectiveness evaluations or as individual value attributes of additional benefit a new technology offers. A separate economic model needs to be developed (typically in Excel) to utilise input data from the clinical studies and other sources.

To support the economic value case for a new pharmaceutical, the instruments used in the trial need to allow the generation of utilities (QALYs). For utility measurement, data from generic health status measures, like the EQ-5D, tend to be preferred by HTA organisations.

For muscular dystrophies, PROs that inform changes in quality of life have been investigated to identify and tailor QoL since at least 2011 [47, 48]. The issue is that the consequences of the disease are broad and diverse, vary from patient to patient and change as a function of age. For the most juvenile patients, outcomes are dependent on parent and physician reports due to a vocabulary limitation common to all young children. To some extent, this can be replaced with the overlapping Bayley III assessment, which can assess neonate responsiveness and functionality while simultaneously evaluating if the child has developmental differences [9]. Bayley III is not a QoL indicator per se, but in the context of neonate development, the comparison between healthy and DMD patients has revealed outcomes that would suggest

that this could be used for the earliest possible assessment. It is essential to read this publication for the indicated outcomes for functional expectation of healthy neonates and how this compares to patients with muscular dystrophy, because of the emphasis that regulatory bodies give to functional gains.

Following this, PROs are obtained routinely using the Paediatric Outcomes Data Collection Instrument (PODCI), SF-36 Health survey [41] and Neuromuscular module and Generic Core Scales of the PedsQL, which are also suggested by the EMA [45]. However, measuring QoL becomes significantly more complex as the patient grows. It has been reported that QoL outcomes using the PedsQL become unreliable as the patient ages [47], at least in the context of restoration of function, as defined by regulatory bodies versus increases in quality of life. The insinuation is that a restoration in function does not necessarily correlate to an increase in quality of life, which reinforces the concept that selected population health-related or additional pathophysiological measurements may need to be integrated into the appraisal as a third axis.

Additional research has been performed utilising the WHO ICF-CY [19, 49, 50], while the most comprehensive research on identifying, designing and optimising PRO specific for the muscular dystrophies has been reported from ScHARR [41–43] that forms a core part of the Project HERCULES initiative, a project led by the patient organisation Duchenne UK, aimed towards creating a suite of disease level HTA evidence including QoL assessment for DMD. The emphasis is that the QoL questionnaire needs to retain core expectations while also expanding the readouts as a function of neurological gain as the patient matures and can expand their expressiveness.

In muscular dystrophies, Project HERCULES (see below) is developing an optimised Duchenne muscular dystrophy (DMD)-specific instrument to create a preference-based measure to meet the needs of HTA.

Besides their use in cost-effectiveness evaluations, the use of generic and condition-specific instruments will generate data to inform HTA decision-makers' assessments of the additional benefit of the new technology compared to the standard of care as individual value attributes.

QoL and functional status data should be collected at baseline and throughout the trial and follow-up period.

We recommend collecting QoL and functional status data using generic health status measures that allow the generation of utilities, as well as including a condition-specific instrument. In selecting which PROMs to choose, it is important to review the trials of the most relevant comparators to enable better comparison between technologies during HTAs.

5.4 The collection of resource use data

This includes hospitalisations, outpatient/GP appointments and tests/investigations to inform the cost-effectiveness analysis. There is no universally recognised method for economic data collection in clinical trials and a variety of techniques are used. The methods and instruments used should reflect the health condition to new technology addresses. The researcher planning the trial should again review the trials of the most relevant comparators to identify potential methods and instruments.

Resource use data should be collected at baseline and throughout the trial and follow-up period. However, resource use data collection from a multinational clinical trial should be performed with caution due to the concerns over the generalisability of the data for country-specific HTA submissions. Hence, there is a key role for local validation of resource use estimates from a trial and/or observational

data collection. Additional Burden of Illness studies should be undertaken alongside trials to show real-world evidence.

5.5 Follow-up time of the trial

Studies should have an appropriately long enough follow-up time to enable the collection of consistent, sufficient and robust data relevant to HTA decision-makers. Minimising uncertainty about clinical effectiveness may be a particular challenge for life-long progressive conditions with limited data such as muscular dystrophies and there is no fixed time period favoured by HTA bodies.

In addition, a plan detailing how and when individual endpoints will be collected is essential. This should include the frequency, methods, sources and time horizon within the data. Besides the data collection plan, the researcher planning the trial should also consider the development of a specific health economics/HTA statistical analyses plan (SAP) covering such aspects as to how PROM and resource use data will be analysed for HTA and use in economic models. This would complement the regular clinical study SAP.

6. HTA scientific advice

Some HTA bodies, for example NICE, offer HTA-specific scientific advice to developers of health technologies to help them develop evidence required for HTAs [51]. Also, the EMA and EUNetHTA (EU body responsible for co-ordinating HTA methods and policies in Europe) offer a joint scientific advice programme to companies with HTA organisations involved.

All of those processes come with varying requirements for preparation and company input and varying levels of opportunities for engagement with the involved parties.

7. Unofficial procedures

1. Advisory board meetings with health economists with clinical trial experience for selected key territories, HTA experts and clinicians to review and input into clinical trials.

2. One-to-one meetings with payer/HTA experts to review and gain input for clinical trial programmes from specific experts for specific regions and/or countries.

3. Working with specialist health economics consultants with clinical trial, HTA scientific advice and HTA experience to review plans, gain input into clinical trials, to develop whole HTA scientific advice programme tailored to the individual company requirements and to provide wider market access and HTA advice also supporting and/or conducting individual projects.

4. Patient and family input is crucial to fully understand the impact of the disease, on health, quality of life, socially and financially as well as any practical considerations relating to the feasibility of the trial design.

For all of the above, we recommend working with health economists with clinical trial and HTA experience to review plans, gain input into clinical trials, to

develop whole HTA scientific advice programme tailored to the individual company requirements and to provide wider market access and HTA advice also supporting and/or conducting individual projects. This can also include the consultants helping the company to navigate the official procedures.

8. Evidence generation alongside and beyond clinical trials

Beyond clinical evidence generation, developers of healthcare technologies need to develop a set of HTA value propositions covering the impact their technology will have on the unmet need, its comparative effectiveness demonstration (planned and expected and/or based on potentially available data), patient reported outcomes (including quality of life), cost-effectiveness, and resource use, costs and budget impact as well as covering a PICO (Patient, Intervention, Comparator and Outcomes) statement.

Companies need to conduct early HTA-specific gap analyses and HTA feasibility assessments to identify gaps in their own as well as their comparator's evidence base to allow for sufficient time to fill those through evidence generation within, alongside and beyond clinical trials. With this, it is also important to remember that HTA preparations need to start early with HTA input into phase II clinical trial planning and designing at the very latest and from there on being a constant and equal (to regulatory) part of any development as getting reimbursement is equally important as getting a marketing authorisation.

9. Other considerations

Companies need to conduct early economic modelling and payer research to inform their pricing strategy reflecting their evidence base. Technologies that are too expensive and do not have a significant benefit over existing alternatives are unlikely to be approved. The key driver of cost in many economic evaluations submitted to HTA organisations is the price of the technology. Where the list price is too high for the technology to be approved for reimbursement, companies can provide discounts and/or other commercial arrangements to reduce the cost to an approvable level. There are also instances when a new technology may be additive to existing standards of care. Where this care is already expensive, it is possible for a new treatment to not be cost-effective even at zero cost [52].

In other instances, it is not the list price of the technology but the uncertainty of the submitted benefits driving the need for a discount and/or commercial arrangement. In HTAs evidence uncertainty is critical and higher the uncertainty the lower the acceptable price will be. Therefore, investing in better data and filling evidence gaps as early as possible can support a better price and avoid the need for a discount and/or commercial requirement.

Economic modelling can help a company to identify the potential need for a discount or commercial arrangement and where they are required the potential magnitude required.

Beyond evidence generation and pricing, manufacturers should follow and engage with HTA developments, follow comparator HTAs to inform their own HTA preparations and be open, transparent, collaborative and realistic when engaging with HTA authorities.

Support is available to companies throughout the whole process from early development through to the conclusion of individual HTAs from official bodies,

like HTA organisations, as well as from experienced HTA expert consultants. Companies should make use of the support available to them.

Furthermore, stakeholders from different backgrounds involved in addressing challenges in healthcare are increasingly working together cross functionally and globally. Developers of treatments for muscular dystrophies should also consider such approaches where they are not already happening. One outstanding example of such a collaboration in muscular dystrophies is Project HERCULES [53, 54].

10. Project HERCULES

In the field of Duchenne muscular dystrophy (DMD), one of the most common and severe forms of muscular dystrophy, Duchenne UK set up Project HERCULES (HEalth Research Collaboration United in Leading Evidence Synthesis) to develop tools and evidence to support HTA for new treatments for DMD [53–55].

Many pharmaceutical companies are developing potential treatments for DMD and are working individually to develop their approach to HTA. The variety of methods in use and the difficulties of generating data can lead to delays in introducing new treatments and inconsistent decision-making.

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 the establishment of Project HERCULES, a collaborative global project bringing together patient organisations, clinicians, academics, nine active pharmaceutical companies, HTA agencies and other advisors.

Project HERCULES has generated a set of disease-level evidence and tools including a natural history model, burden of disease data, a de novo DMD-specific quality of life metric, and a core economic model. These individual workstreams have been developed in parallel through an iterative process enabling evidence generated for one work stream to inform the others. This iterative approach ensured that input from clinicians, patients and carers and other experts was used for multiple purposes minimising the demands on stakeholders.

The leadership of a patient organisation enabled access to data sources and expertise that may be inaccessible for individual or industry researchers. The patient organisation was also able to recruit patients and parents to participate in the research through the use of social media and offline networks. There have been clear efficiencies for manufacturers in being able to access evidence and expertise and a greatly reduced cost compared to developing these evidence and tools in isolation.

The collaborative approach taken by Project HERCULES was not without challenges. Researchers often needed to learn to explain complex concepts in accessible language to ensure patients and lay members could effectively contribute. Balancing the input from patients and families with clinical, industry and HTA experts has also been challenging. Project HERCULES selected researchers in part by their readiness to work collaboratively with stakeholders ensuring that they were working closely with the other research teams and actively listening and responding to all the information obtained, and not simply seeking confirmation for what they expected to find.

Despite the challenges, Project HERCULES has consistently taken a collaborative approach that has had a clear impact on each workstream:

- 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 transfer state between the traditional stages of late ambulatory and early non-ambulatory. Patient and parents told researchers about the importance of being able to weight bear for a period following the loss of ambulation. This state has been incorporated into the natural history model, which informs the other work streams.

- Development of a bespoke Quality of Life 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 clinicians, patients and families

- A burden of illness study focusing on what is most important to clinicians, patients and families.

11. Impact on investment and return on investment

In healthcare, and particularly therapeutic intervention, development takes a long time, typically over 14 years [56, 57], and is costly (up to $2.6 billion, [58]), which means that significant risk has to be carried for a long duration before knowing if the product was worth the investment. However, in the context of rare diseases, the scenario is significantly different. Whereas the development up to launch of a medicine for a very common condition may cost $2.6 Billion, for the muscular dystrophies the value might be closer to $400 Million. The number of patients involved in the trials are significantly lower, the duration of the trials shorter and upon market release, an extensive sales force is not necessary, as patients are typically referred to centres of excellence [59–61], and clinicians who focus on treating patients with rare diseases are typically well versed in developments in the field, while patients associations perform stellar work in communicating with patients and their supporters what is happening [7, 62–68]. As explained above, achieving a marketing authorisation does not guarantee reimbursement that companies need to achieve before they can realise uptake and sales.

This leads us to two questions: (a) what impact integrating HTA requirements in clinical trial design has on investment decision-making, and (b) what impact it has on return on investment.

To answer the first question, we need to look at how pharmaceutical investment decisions are informed.

The decision to invest in the creation of a medical product, as for all other businesses, hinges on the definition of the market size, the terminal market value. The terminal market value is then reverse calculated to the potential present value by integrating in phase specific costs, risks and probabilities of success to give a net present value (NPV). If the NPV is positive, then the innovation is considered worthwhile to invest in, whereas if it is negative, the rule of thumb is to not invest.

NPV calculations are only as good as the data used to generate them, and both accurate and comprehensive values ideally should be used, based on real market dynamic, the latest clinical success rates and considering the latest reimbursement approaches (such as HTAs). Thus, designing clinical trials that are more likely to result in better data and addressing HTA evidence requirements improve NPV calculations and thus optimise investment decision-making [69]. However,

it is important to state that there is the possibility that market authorisation agencies and reimbursement bodies may not accept clinical data from other jurisdictions due to different standards and regulations. Therefore, while NPV outputs are additive, the developer may need to assess if different clinical trials need to be performed in different locations and if and how the data can be used within a comprehensive evidence dossier that can be submitted to as many different agencies as possible.

The answer to the second question is that investing in better evidence generation will lead to higher chances of gaining desired reimbursement at the desired price, thus unlocking market access and sales potential early, thus having a positive impact on ROI. For the rare diseases, accounting for post-marketing surveillance, manufacturing and general admin costs, to reach a balance of zero, the product will need to generate at least $1 Billion in life time sales; to enable the innovators to sustain and expand their pipeline, generating additional new interventions for other rare diseases, life time sales between $2 Billion and $8 Billion would be required. Based on marketing authorisation restrictions on recently approved DMD interventions, that are based upon the differing forms of dystrophinopathies, this revenue level would need to be generated from generating a beneficial effect (clinical effectiveness and cost effectiveness) for 10% of the muscular dystrophy population, who would likely need to administer the solution every year for the rest of their life, that could be an additional 25 years based on the increased standards of care. This combined information is then used to define the agreed price of the solution with the reimbursement agency, within the specifics of the healthcare system and marketplace in each different geography (this can be an entire country or a region within a country).

Governments have tried to be flexible to account for the market risks, policy changes have been implemented, such as the orphan drug definition in the EU. Because of the potentially low revenue potential, investing in solutions for rare diseases carries a higher risk, as costs cannot be recovered, therefore acts that provide market exclusivity for 12 years for paediatric diseases, in competition with 'similar competitive products'. Additionally, to facilitate R&D in healthcare, most countries offer R&D tax credits, independent of the source of the R&D funding, and using a very broad definition of what constitutes a R&D cost to stimulate such endeavours. These credits can be used to offset taxes on profit, providing the entity reinvests the revenue.

Conceptually for a paediatric rare disease, the rule may need to be revisited to reconsider what is the definition of a similar product to provide clarity to innovators. Arguably it is any intervention that offers disease correction, which can be a very broad definition or is it based upon similar mechanisms of action; ideally innovators would need this point clarified to enable better clinical trial design. This is reflected in the clinical trials that are ongoing and appear to be following the conceptual design associated with major diseases, that is an 'all or nothing' response based upon the intervention being assessed.

Given that the disease takes years to manifest itself, and varies significantly from patient to patient as seen in other progressive degenerative diseases or traumatic injuries with inconsistent and differing measurements, it is more likely that a spectrum of concepts and solutions need to be integrated together as function of the patient and the tissue damage at that specific stage within the complete disease progression to provide beneficial outcomes; this is likely going to include standard chemical entity interventions, anti-inflammatories and physiotherapy and potentially stem cells, biomaterials, genetic correction, tailored and designed as a comprehensive intervention solution tailored to the patient and their population health status.

12. Conclusions

In summary, we would like to emphasise that for a product to be able to get a positive HTA recommendation leading to reimbursement by payers, manufacturers need to carefully consider the evidence needs of HTA authorities when planning clinical trials and evidence generation programmes.

For each new product, this should start early, that is when planning phase II trials, and continue throughout the clinical development process in order to optimise the chances of gaining reimbursement and consequently return of investment.

Beyond evidence generation and pricing companies follow and engage with HTA developments, follow comparator HTAs to inform their own HTA preparations and be open, transparent, collaborative and realistic when engaging with HTA authorities.

Support is available to manufacturers throughout the whole process from early development through to the conclusion of individual HTAs from official bodies, like HTA organisations, as well as from experienced HTA expert consultants. Additionally, innovative initiatives, such as Project HERCULES, are existing to support developers but also serve as examples of what is possible and can be done beyond existing support structures and options. Manufacturers should make use of the support available to them.

Furthermore, addressing the evidence requirements of payers and HTA organisations in clinical trials and other evidence generation can lead to improved investment decision-making and have a positive impact on ROI.

It is also important to emphasise that developers of healthcare technologies need to address the evidence needs of reimbursement decision-makers early and throughout the development process in order to optimise their chances of gaining market access at a desired price unlocking ROI. To obtain and support this outcome, there may need to be a reconfiguration of the muscular dystrophy R&D ecosystem. A large amount of fundamental research has been and is still performed in the muscular dystrophies, mostly paid by charities such as MDA, Telethon, Duchenne and AFM, to name only a few. In no way does the volume of research and funding for muscular dystrophy compare to the major diseases.

For the major diseases, the years of highly funded fundamental research has resulted in outcomes that have translated to the clinic for the benefit of patients that is founded upon a significant amount of independently validated and reproduced data. Naturally, at the public funding level, policy is therefore biased towards encouraging fundamental research to have a translatable dimension to justify to the taxpayer the expense.

Rare disease researchers have not had a large knowledge resource but find themselves in the position that they need to accelerate their translatable research, due to patient need, without the same foundation of knowledge to rely upon. This is not going to change; however, different approaches to managing the knowledge that is generated from the limited financial support that is given to fundamental research in the muscular dystrophies would be beneficial for this field, other muscular diseases and the rare diseases field as a whole. But the barriers to progression are compounded by additional characteristics that are common to all other diseases and the culture of R&D and others that are unique to the field of muscular dystrophy.

One significant issue in knowledge generation in the muscular dystrophies is the genotypic diversity within each type that often prevents statistically relevant insights being obtained that can be leveraged into intervention development. This is because to obtain some level of relevant data the work has to be performed in an animal model that corresponds to the specific disease genotype. This means

creating the model (often a mouse) through transgenic modification, and after stabilising the model, assessing if the genotypic change generates a disease phenotype that corresponds to the human form of disease. On the proviso that a comprehensive understanding of the disease progression and phenotype is understood in the human.

Pre-clinical modelling is used to generate data that show a corrective effect, levels of toxicity, intervention metabolism and potential dosing. After generation of the comprehensive dossier for review, a positive ethical review board will then permit a phase I testing of the drug in humans. The aim is to define if the considered therapeutic dose is toxic to a healthy human. If it is confirmed that the therapeutic does not harm a human, it is then approved to test in a small population of patients if in addition to not harming the patient it confers some level of corrective effect (phase IIa). If positive, the study can be expanded to more patients (phase IIb). Positive data from this phase enable the larger scale phase III, efficacy study on large patient populations. For diabetes and CVD, the available patient population for recruitment is huge.

For muscular dystrophies it is not; this means that a substantial amount of evidence has to be generated from between 30 to 250 patients, if they correspond to the inclusion/exclusion criteria of the trial, which typically includes not taking other experimental interventions. Independent of whether a disease is rare or frequent, this is not possible. It would be impossible and likely rejected by market authorisation bodies if this approach was taken for a highly prevalent disease as an evidence collection method. Policy changes have occurred focusing on rare diseases to be more flexible on effect and patient numbers, but clinical trial design still hinges on an 'all or nothing' therapeutic effect from a single intervention. This does not correspond to the complexity of muscle tissue, the diversity between patients, the impact of comorbidities and the regenerative characteristics of muscle.

For fundamental researchers, specifically those in academia who perform most of the fundamental research operate in a 'publish or perish' professional environment. The nature of fundamental R&D is that >90% of the data generated, at first glance, is a negative result, and the space limitations in articles accepted for publication means that even very limited positive results are shown. A negative result being defined as an outcome that does not correspond to enabling a chosen question to be answered, it does not mean the data are useless or invaluable.

With such limited resources, financially, biologically and clinically, but with such a clear patient need, the field needs to reconsider how it best leverages its data, especially as there are not a high number of researchers active in muscular dystrophy, in comparison to cancer or cardiovascular diseases.

This could be resolved through a 'research data' database that can be accessed by all accredited researchers to enable searching other historical data from other sources to look for concepts that did not work to prevent wasteful repetition, or to look at the unpublished data with a new perspective to enable a different insight. This also needs to happen with clinical data, from those patients in trials to those having their disease history mapped, albeit with a greater ethical oversight. There are nearly 13,000 patients presently in global clinical trials for Limb Girdle, Beckers and Duchenne muscular dystrophy who will be generating what may first appear to be non-relevant data related to the defined outcomes, but it is very likely that in the context of age, disease progression, biometrics, comorbidity status, mental health status, population health characteristics as well as response to intervention, these data are going to massively inform the field and globally standardised clinical care pathways and patient biometric measurements.

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