Master's Degree Dissertation

Cost-effectiveness análisis ofmicro-dystrophin: a novel gene therapy for duchenne muscular dystrophy

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I formally declare that I have written the submitted piece of work independently. I did not use any outside support except for the quoted literature and other sources mentioned in the paper.

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ABSTRACT

Background: Gene therapies offer ground-breaking new opportunities for the treatment of rare and genetic diseases, however they also cause great concern among payers due to their skyrocketing costs. A novel gene therapy for Duchenne Muscular Dystrophy (DMD), called AAVrh74.MHCK7.micro-Dystrophin (micro-Dystrophin), is currently being analysed in phase I/II clinical trials and, up to now, it has shown very positive and encouraging results.

Objective and hypothesis: The purpose of this study is to calculate the maximum price at which micro-Dystrophin would be cost-effective for treating patients diagnosed with DMD in a UK setting over a lifetime horizon from both, a/the healthcare and a/the societal perspective. Given the positive results of the ongoing clinical trials, we hypothesize micro-Dystrophin to be cost-effective at a price of $1M.

Methods: A Markov state–transition model was developed to estimate the costs and effectiveness of micro-Dystrophin compared to the best supportive care (BSC). Costs (in 2019 USD), utility data (in quality-adjusted life-years) and transition probabilities for BSC were obtained from the literature. Transition probabilities for micro-Dystrophin were assumed from the phase I/II clinical results. The incremental cost-effectiveness ratio (ICER) was calculated and one-way sensitivity analyses were performed to test the robustness of the results.

Results: From the/a healthcare perspective and assuming a price of 1M$, micro-Dystrophin compared to BSC, resulted in an increase of approximately $1M in costs, 4 QALYs and an ICER of $264,000; whereas from the/a societal perspective, it resulted in an increase of $1,1M in costs, 8 QALYs and an ICER of $141,000.

Conclusion: At a price of $1M, micro-Dystrophin would not be cost-effective from the/a healthcare perspective in the UK. The price should be set at around $440,000 to fall within the cost-effectiveness threshold for ultra-rare diseases and get a favourable recommendation for reimbursement by NICE.

INTRODUCTION

Gene therapy marks a new era for the treatment of human diseases. After three decades of intense research, failures and disappointments, gene therapies are now reaching the market. Gene therapy can be defined as modifying or introducing new genetic material into a person's DNA to treat, prevent or cure a disease. This can be done by either adding a healthy copy of the mutated gene that causes the disease or by repairing the mutation. Gene therapy aims to correct the underlying cause of a disease instead of just treating the symptoms and therefore, it is regarded mostly as a one-time therapy, although in some cases it may require more than one dose to cure the disease entirely (1).

Currently there are only five genetic diseases being treated with gene therapies approved either/or by the U.S. Food and Drug Administration (FDA) and the European Medical Agency (EMA). However more than a 100 diseases are being explored for potential treatment using this approach (2, 3). One of these diseases is Duchenne Muscular Dystrophy (DMD). DMD is a genetic rare disorder caused by mutations in the *dystrophin* gene that result in loss of the dystrophin protein, which is indispensable for the function of muscle fibers (4). DMD is among the most common single-gene disorders in humans, with an incidence of 1 in 3500 to 5000 newborn boys, and an estimated prevalence of 4.8 per 100,000 males worldwide (5).

People with DMD suffer from progressive muscular damage and degeneration, resulting in muscular weakness, associated motor delays, loss of ambulation, respiratory impairment, and cardiomyopathy. Death usually occurs as a result of cardiac or respiratory muscle deterioration during adolescence (6).

There is no cure for DMD and the standard of care consists on corticosteroids (predominantly prednisolone and deflazacort) together with the alleviation of symptoms and management of complications. The implementation of advanced supportive care such as assisted ventilation (non-invasive and invasive), spinal surgery, and prevention

and management of cardiomyopathy-related heart failure has prolonged patients' life into their 30s or 40s (7-9).

In addition to the standard of care, there are currently two drugs authorized to specifically treat DMD: Eteplirsen (or Exondys51 by Sarepta Therapeutics), which received FDA approval in 2016 (10), and Ataluren (or Translarna by PTC Therapeutics), which received EMA conditional authorization in 2014 (11). However, these drugs are indicated for small sub-populations of DMD patients. Exondys51 is indicated for patients with a specific mutation that is amenable to exon 51 skipping, which only comprises 13% of the patients, while ataluren is indicated for patients with non-sense mutations, which are about 15% (10, 11).

Accordingly, there is an acknowledged urgent need for a therapy that has the potential to benefit a larger proportion of DMD patients; and here is where gene therapy comes into play. By delivering a functional copy of the *dystrophin* gene to the muscle fibers of DMD patients, muscular damage and degeneration could be delayed and in the best scenario, even prevented.

Nowadays several gene therapies for DMD are being developed and tested by different companies. The most promising and advanced one is AAVrh74.MHCK7.micro-Dystrophin (also named SRP-9001), designed by a team at the Nationwide Children's Hospital (Columbus, Ohio) and licensed by Sarepta Therapeutics. This therapy uses a virus (AAVrh74) and a specific muscle promoter (MHCK7) to deliver *micro-dystrophin* to the skeletal and cardiac muscle fibers. *Micro-dystrophin* is a shorter version of the *dystrophin* gene, that contains the key elements of the gene needed to produce a functional dystrophin protein (12). Two clinical trials are undergoing to evaluate the safety and efficacy of micro-Dystrophin: a Phase I/IIa (NCT03375164), with 4 patients enrolled (13) and a Phase II (NCT03769116), with 24 patients enrolled between 4 and 7 years old and looking to enrol 16 more patients to increase the study power (14).

Last March, Sarepta Therapeutics presented positive preliminary results of the ongoing Phase I/IIa trial, and is hoping to confirm these results in the new Phase II trial. The results showed (15):

- Robust expression of transduced *micro-dystrophin* in muscle fibers from the gastrocnemius in all 4 patients at day 90. The mean intensity of the fibers was 96% compared to normal control.
- Robust levels of micro-dystrophin as measured by Western Blot at day 90 (74.3% to 95.8% compared to normal control).
- A mean of 1.6 vector copies per cell nucleus, consistent with the high *micro-dystrophin* expression levels observed.
- Significant decreases of serum creatine kinase (CK) levels, with a mean reduction of 63% at day 270. CK is an enzyme associated with muscle damage.
- No serious adverse events.
- Consistent and persistent improvement of the functional motor abilities measured by the North Star Ambulatory Assessment (NSAA), from baseline to day 270.

Although these results are preliminary and need to be reproduced in additional patients, they represent an unprecedented advancement in the treatment of DMD. With such a good scenario, potential commercialization is likely to happen over the next 1-2 years and this brings up the question: how much could micro-Dystrophin cost?

Gene therapies for rare diseases already available in the market are extremely costly (Table 1).

Name	**Disease**	**List price** (in 2018 currencies)
GLYBERA	Reverse lipoprotein lipase deficiency (LPLD)	€1.2 million (already withdrawn from the market)
LUXTURNA	Inherited retinal dystrophy	$425,000 per eye, or $850,000 per patient (in the US). EU price has not been disclosed yet.
STRIMVELIS	Severe combined immunodeficiency (ADA-SCID)	€594,000 or $648,000. Only approved by the EMA.
ZOLGENSMA	Spinal muscular atrophy (SMA)	$2.1 million ($425,000 a year spread out over five years*). Only approved by the FDA.
ZYNTEGLO	Transfusion-dependent β-thalassemia (TDT)	€1.575 million or $1.77 million. Only approved by the EMA.

Table 1: Price of the gene therapies approved by EMA and/or FDA for rare diseases (2, 3).
*Price in 2019 currency.

These prices set a precedent for other gene therapies in development. Sarepta Therapeutics has yet to announce the list price at which they are planning to commercialize micro-Dystrophin, but it is expected it to be in a similar range.

The aim of this study is to estimate the cost-effectiveness of the gene therapy micro-Dystrophin compared to the best supportive care (BSC) in a UK setting over a lifetime horizon from both: a healthcare perspective and a societal perspective, in alignment with ICER's Value Assessment Framework for Ultra Rare Diseases (16).

In 2016, the National Institute for Health and Clinical Excellence (NICE) in the UK proposed a cost-effectiveness threshold for Highly Specialised Technologies (HST), which target diseases with a prevalence of two per 100,000 population or less (approximately 1,300 individuals in the UK). This threshold was set at £100,000 per QALY for treatments that deliver fewer than 10 QALYs to the patient in their lifetime. The threshold can rise to £300,000 for therapies that deliver more than 30 additional QALYs to the patient in their lifetime. This is 5 to 15 times higher than the range of £20,000-30,000 used for non-specialised technologies (17, 18).

Taking NICE's threshold for HST into account, the aim of this study is to calculate the maximum price at which micro-Dystrophin would be cost-effective in a UK setting from a/the healthcare perspective. Given the positive results of the ongoing clinical trials, we hypothesize a price of $1.000.000 to be cost-effective.

METHODS

Model framework

A deterministic Markov state–transition model was generated to evaluate the cost-effectiveness of micro-Dystrophin vs best supportive care (BSC) in patients with DMD in a UK setting. The model was developed in accordance with the ISPOR-SMDM Modeling Good Research Practices Task Force (19).

The model comprises five health states: (1) early ambulatory: approximately age 5–7 years; (2) late ambulatory: approximately age 8–11 years; (3) early non-ambulatory: approximately age 12–15 years; (4) early non-ambulatory: approximately age 16 years or older; and (5) an absorbing state for dead (Figure 1), based on stages of disease as described in the international DMD clinical care guidelines (8).

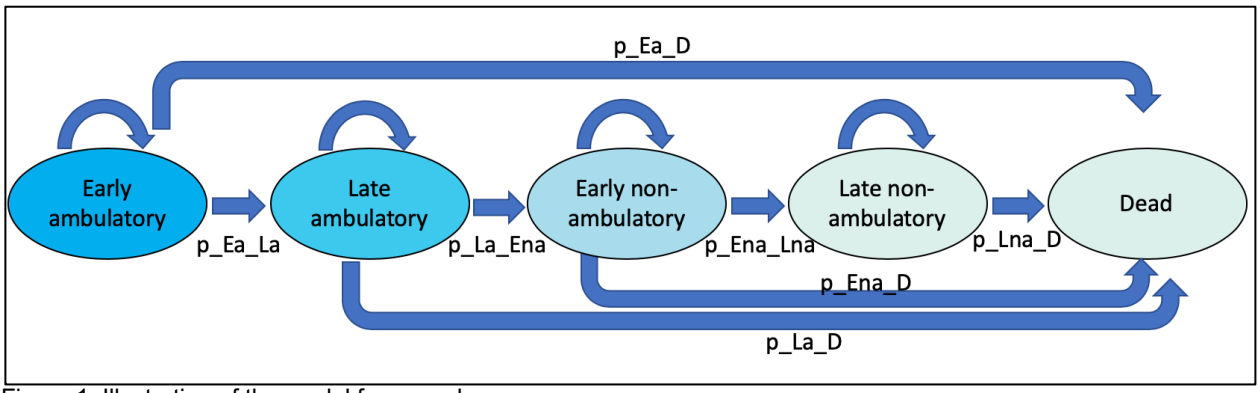

Figure 1: Illustration of the model framework

The model starts with a hypothetical cohort of patients of DMD at the early ambulatory stage that begin treatment at the age of five years given that diagnosis usually occurs around age five. The model was used to project total costs and quality-adjusted life years (QALYs) over a lifetime time horizon (or a maximum age of 85 years), with an annual cycle length. Costs and outcomes were discounted at 3.5% per year. A half-cycle correction factor was applied to costs and outcomes, as recommended by the ISPOR-SMDM Modeling Good Research Practices Task Force (19). Excel 2016 was used to generate the model (see Annex I for the excel document).

Transition probabilities

The patients can transition from the current state to next more severe one, die or remain in the current state. The probabilities of transition were obtained from different published studies (20-22). For BSC, it was assumed that, on average, patients transition every 4 years to the following phase. Starting the model at an age of 5 years, this corresponds to an annual transition probability of 0.16, as stated in (20). At this rate, the probability of transitioning to the non-ambulatory is around 50% at age 15 years, which is in accordance with published reports (23).

Transition probabilities for the micro-Dystrophin treatment were assumed from the clinical outcomes of the currently ongoing phase I/IIa trial, since there is no evidence for how micro-Dystrophin could affect the time spent in each phase. We assumed that treatment with micro-Dystrophin would extend the time spent in the first phase, the early ambulatory phase, by 10-15 years. The reasons for that are:

- The results of the ongoing phase I/IIa trial show consistent and persistent improvement of the functional motor abilities measured by 4 different assessments: 1. the North Star Ambulatory Assessment (NSAA), 2. Time to rise, 3. Four stairs up, 4. 100m walking (15). Therefore, it was assumed that patients would stay in the ambulatory state as long as micro-Dystrophin is being produced by the targeted muscle cells.
- Micro-Dystrophin would most likely be produced throughout the lifespan of the targeted muscle cells, which is an average of 15 years for skeletal muscle cells (24). The carrier of micro-Dystrophin, the AAV, does not integrate into the host genome, which means that an injection of AAV-micro-Dystrophin at the age of 5 would lead to efficient production of micro-Dystrophin until the targeted muscle cells get renewed, approximately at the age of 20. Patients would therefore transition to the late ambulatory phase around 20-25 years old (Figure 2).

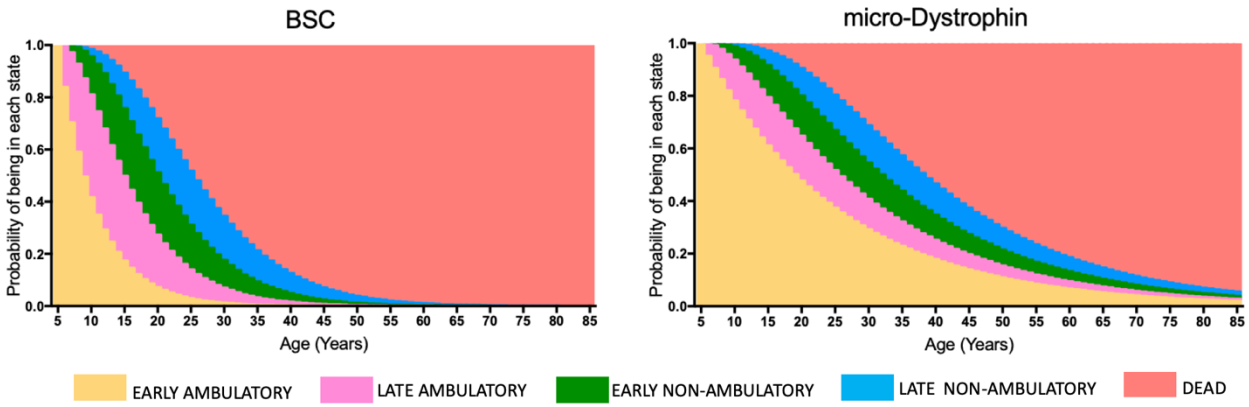

Figure 2: Probabilities of being in each stage at different ages

Health State Utilities

Health state utilities (ranging from 0=dead to 1=perfect health) were taken from previous analyses (20, 21, 25, 26). Patient utility scores were based on the Health Utility Index (HUI; proxy assessed by the primary caregivers), which includes 16 questions encompassing eight dimensions (hearing, speech, ambulation/mobility, pain, dexterity, self-care, emotion and cognition) (25, 27). Disutility values due to possible side effects were not included in this model.

Caregiver utilities were assessed using the EuroQol EQ-5D-3L, which is a generic HRQL instrument covering five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) (28).

Health state	Utilities				Source
	Patient		Caregiver		
	Mean	SE	Mean	SE	
Early ambulatory	0.70	0.04	0.86	0.02	(20, 21, 25, 26)
Late ambulatory	0.61	0.03	0.84	0.02	(20, 21, 25, 26)
Early non-ambulatory	0.22	0.01	0.78	0.02	(20, 21, 25, 26)
Late non-ambulatory	0.15	0.01	0.81	0.02	(20, 21, 25, 26)

Table 2: Utility scores in each stage

Costs

Costs data was obtained from (29) (see Annex II for detailed information). Costs include:

- Direct medical costs (hospital admissions, visits to physicians and other healthcare professionals, medical tests and assessments, medications, and emergency and respite care).
- Direct non-medical costs (costs associated with non-medical aids and investments) and costs associated with informal care (paid and unpaid informal care by the primary caregiver).
- Indirect costs (production losses for the patient and primary caregiver due to absenteeism and impaired productivity while working).

Health state	Direct costs				Indirect (productivity costs)				Total cost		Source
	Medical		Non-medical		Patient		Caregiver				
	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	
Early ambulatory	17472.08	229.25	15949.21	81.87	0.00	0.00	11757.22	311.12	45178.51	573.12	(20, 29)
Late ambulatory	18323.58	163.75	18700.20	81.87	0.00	0.00	13656.72	245.62	50680.50	425.75	(20, 29)
Early non-ambulatory	27002.31	474.87	29245.68	180.12	0.00	0.00	20976.32	605.87	77224.31	1162.62	(20, 29)
Late non-ambulatory	45178.51	556.75	27526.31	147.37	23301.57	2521.74	18405.46	425.75	109253.73	2619.99	(20, 29)

Table 3: Model costs in 2019 USD. Data are presented as mean (standard error). Source cost estimates were converted from 2015 Great British Pounds to US dollars using the 2015 exchange rate average (1 GBP = 1.5162 USD) and inflated from 2015 to 2019 values using consumer price data from the Organisation for Economic Cooperation and Development (increase from 1 USD to 1.08 USD).

The cost of micro-Dystrophin was set at $1M for a one-time infusion at the age of 5.

Perspective of Analysis

The model was used to estimate the cost-effectiveness of micro-Dystrophin at an assumed price of $1,000,000 per patient, from both a healthcare perspective and a societal perspective.

The base-case analyses were performed from the healthcare perspective and included only direct medical costs and patient utilities. The analyses from the societal perspective included all costs and utilities from patients and caregivers.

Model validation

Model validation was done by comparing it to similar models (20, 21). The following factors were compared:

- The Markov traces showing the probability of staying in each state for BSC.
- The outcomes: costs and QALYs for BSC.

Sensitivity Analyses

Deterministic one-way sensitivity analyses were performed of the base-case model, from both the healthcare and societal perspective, to test the robustness of the model. See Figure 3 with corresponding tables of the parameters analysed and high and low input values.

RESULTS

From a/the healthcare perspective and assuming a price of $1M, micro-Dystrophin treatment resulted in an increase of approximately $1M in costs and 4 QALYs (Table 4) compared to BSC; whereas from a/the societal perspective, it resulted in an increase of a little bit over $1M in costs and 8 QALYs (this increase in QALYs is due to the inclusion of caregiver's utilities) (Table 5).

From a/the healthcare perspective, the base-case result for the incremental cost-effectiveness ratio (ICER) comparing micro-Dystrophin (at a cost of $1M) to BSC is around $264,000 (Table 4). This value represents a cost-utility result beyond the threshold accepted by NICE of approximately $125,000 (£100,000) per QALY, for HST that deliver less than 10 QALYs to the patient during lifetime (17, 18). The value-based price of micro-Dystrophin was calculated for different thresholds (Table 6). To be cost-effective at a $125,000/QALY (£100,000/QALY) threshold and receive a favourable recommendation from NICE, the list price of micro-Dystrophin should be set at around $443,000 (Table 6).

From the societal perspective, the ICER is around $141,000 (Table 5), almost in the range of NICE accepted thresholds.

HEALTH STATE	MEDICAL COSTS		OUTCOME (QALYs)	
	BSC	Micro-Dystrophin (cost of $1000000)	BSC	Micro-Dystrophin
EARLY AMBULATORY	$83,690	$1,208,864	3.35	8.36
LATE AMBULATORY	$77,896	$54,971	2.58	1.82
EARLY NON AMBULATORY	$83,257	$65,004	0.69	0.54
LATE NON AMBULATORY	$114,293	$89,007	0.37	0.29
DEAD	$0	$0	0.00	0.00
TOTAL	$359,136	$1,417,846	6.99	11.00
INCREMENTAL		$1,058,710		4.02
ICER		**$263,673**		

Table 4: Base-case results from the healthcare perspective for micro-Dystrophin compared to BSC. Micro-dystrophin price was set at $1M.

HEALTH STATE	MEDICAL COSTS		OUTCOME (QALYs)	
	BSC	Micro-Dystrophin (cost of $1000000)	BSC	Micro-Dystrophin
EARLY AMBULATORY	$216,401	$1,540,072	7.46	18.61
LATE AMBULATORY	$215,450	$152,042	6.15	4.34
EARLY NON AMBULATORY	$238,107	$185,906	3.11	2.43
LATE NON AMBULATORY	$276,392	$215,242	2.42	1.88
DEAD	$0	$0	0.00	0.00
TOTAL	$946,351	$2,093,261	19.13	27.26
INCREMENTAL	$1,146,911		8.13	
ICER	**$141,086**			

Table 5: Base-case results from the societal perspective for micro-Dystrophin compared to BSC. Micro-Dystrophin price was set at $1M.

	Price to achieve $37,500/QALY (£30,000/QALY)	Price to achieve $62,5000/QALY (£50,000/QALY)	Price to achieve $125,000/QALY (£100,000/QALY)	Price to achieve $375,000/QALY (£300,000/QALY)
Healthcare perspective	$91,862	$192,243	$443,195	$1,447,004
Societal perspective	$157,932	$361,160	$869,232	$2,901,517

Table 6: Prices for micro-Dystrophin to meet specific incremental cost-effectiveness ratios.

One-way sensitivity analyses were performed for key drivers of variability and uncertainty from both, the healthcare and the societal perspective. Inputs that were changed included: the time horizon, the costs, the discount rate and the probability of transition and utilities for the micro-Dystrophin treatment at the early ambulatory phase (Figure 3).

As shown in the tornado diagram (Figure 3), which depicts multiple one-way sensitivity analyses, variation of the time horizon and discount rate are the inputs with the most sensitivity in the model. Reducing the time horizon to 15 years instead of a lifetime strongly influences the results, mainly due to the minor increase in QALYs. The longer the time horizon, the lower the ICER reached. As expected, a discount rate of 5% resulted in reduced costs and outcomes for both BSC and micro-Dystrophin; and in an increase of the ICER. Instead, a discount rate of 0% had the opposite effect.

A 25% increase or reduction of the medical costs (for the healthcare perspective) and the total costs (for the societal perspective), did not result in substantial ICER variations.

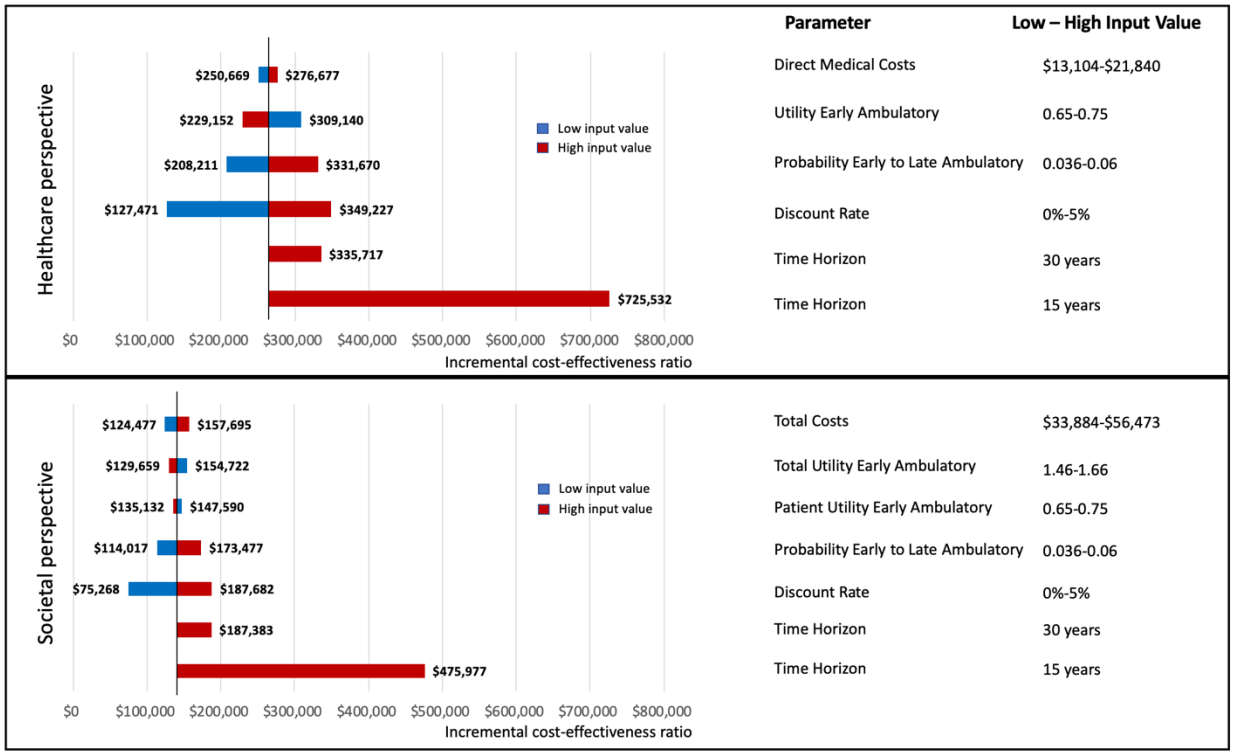

Figure 3: Tornado diagrams for one-way sensitivity analysis of inputs on the base-case ICER of micro-Dystrophin versus BSC from the healthcare and the societal perspective.

The utility of the early ambulatory phase with micro-Dystrophin treatment was also analysed in the sensitivity analysis. Given that the patients of the ongoing clinical trials are showing improved functional motor abilities, it is possible that the utility score of the first phase of the disease increases, and consequently the utility of the caregivers too. A patient utility of 0.75 (instead of 0.7) resulted in an ICER of approximately $229,000 from the healthcare perspective. An increase of the total utility from 1.56 to 1.66 resulted in an ICER of approximately $130,000 from the societal perspective.

And lastly, we analysed the probability of transitioning from the early ambulatory phase to the late ambulatory phase with micro-Dystrophin, given that it is a key driver of uncertainty. By reducing 25% the probability of transitioning from the 1st to 2nd phase (0.036 instead of 0.048), which would extend the early ambulatory phase nearly 5 years,

micro-Dystrophin at a price of $1M would be almost cost-effective (ICER≈$208,000) from the healthcare perspective. By increasing the same probability to 0.06 to account for side effects and reduced expression of micro-Dystrophin in muscle cells, the ICER increased to approximately $332,000.

DISCUSSION

This model, which was based on previously published cost and utility data (20, 21, 25, 26), showed that, at a price of $1M, micro-Dystrophin would not be cost-effective from the healthcare perspective. The price of micro-Dystrophin should be set at around $440,000 to be cost-effective at a $125,000 (£100,000) threshold.

This price would be lower than current available gene therapies (Table 1). For instance, the price of Zolgensma to treat spinal muscular atrophy, was set by the manufacturer at $2.1 million ($425,000 a year spread out over five years), being the most expensive drug currently in the market. Zolgensma list price would likely be rejected by NICE given that at $2M, the cost-effectiveness threshold was $243,000 (30). The analysis made by the 'Institute for Clinical and Economic Review' indicated that it would have to have its price reduced to under $900,000 for a one-time administration to meet a $150,000 per QALY threshold (30). This precedent might therefore encourage Sarepta Therapeutics to set a price of over $1M for micro-Dystrophin in the US. However, in the UK, NICE is unlike to consider such a cost. The highest price the NHS is nowadays reimbursing for a gene therapy is £505,000, for Strimvelis for the treatment of the rare disease ADA-SCID (Table 1) (31). According to the results of the present study, micro-Dystrophin would be cost-effective at a price of $440,000. Setting the price around this number would maximise the probability of acceptance for reimbursement by NICE.

From a/the societal perspective, a price of $1M resulted in an ICER of $141,000, almost in the range of NICE´s accepted threshold ($125,000). The lifetime costs from the societal perspective were almost 2.6 times higher than costs from the healthcare perspective. The

economic value of the informal caregiving time, which is mostly provided by family members, represents a large proportion of the total cost of the disease. In the UK, the indirect and informal care costs account for approximately 47% of the total costs (29). Thus, for a significant economic evaluation of treatments for childhood chronic diseases like DMD, guidelines should call for the inclusion of all costs.

The current decision model was validated in terms of comparisons to previously performed economic evaluations (20, 21). These studies aimed at assessing the cost-effectiveness of the following treatments compared to BSC: (1) a hypothetical treatment that slows disease progression by 25% and costs $130,000 per year (total of approximately $1.9M during the lifetime of the patient) (20), and (2) the exon-skipping therapy eteplirsen. Eteplirsen (EXONDYS 51) was approved by the FDA in September 2016 for patients with mutations amenable to skipping of exon 51 (approximately 13% of the DMD population) and has an annual treatment cost of around $1M (21).

The base-case results used in this study including the total lifetime costs and utilities for the BSC from both the healthcare and societal perspective were very similar to both analyses mentioned above. However large differences were found in the lifetime costs and utilities of the treatments modelled. The hypothetical treatment analysed in (20) resulted in a very small increase of patient utility (0.79 QALYs) and therefore a large incremental cost-effectiveness ratio (approximately 2M GBP (in 2015 GBP)). Similar results were found by the ‘Institute for Clinical and Economic Review’ when assessing the lifetime cost-effectiveness of eteplirsen (21). The report stated that the treatment resulted in small increases of dystrophin levels in the muscle fibers of the patients and no moderate or high-quality evidence of functional benefits. Therefore, in the absence of clinical evidence of benefit and such high annual costs throughout a patient’s life, the incremental cost-effectiveness ratios were extremely high (approximately $2M).

In contrast, the incremental cost-effectiveness ratio of micro-Dystrophin at a cost of $1M was about $263,000 from a/the healthcare perspective, 8 times lower than the previous mentioned ratios. The main difference lies in the reduced transition probability from the early to the late ambulatory phase with the micro-Dystrophin treatment. In this model, it

was assumed that patients would stay in the early ambulatory phase for 10-15 years longer than BSC-treated patients given the positive clinical outcomes of the currently ongoing phase I/IIa trial. The clinical outcome of micro-Dystrophin has already been shown to be significantly higher than eteplirsen´s: 95% dystrophin positive fibers with micro-Dystrophin vs 0.44% with eteplirsen compared to normal control (15, 21). These results together with the fact that micro-Dystrophin is administered by a single infusion (instead of weekly infusions of eteplirsen), greatly reduces the cost of the treatment and increases the outcome.

The current decision model has several limitations that need to be considered when assessing its relative generalizability.

First, the lack of long-term clinical outcomes in current clinical trials of micro-Dystrophin drove the main assumption of the model: the reduction of the transition probability from the early to the late ambulatory phase from 0.16 to 0.048. The positive impact of micro-Dystrophin was limited to an extension of 10-15 years of the early ambulatory phase only. This is a conservative assumption for micro-Dystrophin given that the renewal rate of cardiomyocytes, the cardiac muscle cells, is much lower than that of skeletal muscle cells. At the age of 50, 60% of the cardiomyocytes of an individual remain from birth (32). Therefore, production of micro-Dystrophin in the targeted cardiomyocytes of DMD patients could be sustained until death. This decreases the probability of patients to dye from heart failure and thus, treatment with micro-Dystrophin would most likely also prolong the latest stage of the disease, the late non-ambulatory phase. However, for simplification of the model and given the lack of evidence in humans, this hypothesis was not considered.

Second, the extension from the early to the late ambulatory phase with micro-Dystrophin led to some overestimation of survival in the tails. 5% of patients would still be alive at 85 years old, which is quite unlikely. Defining transition probabilities by age groups would reduce this overestimation. However constant lifetime probabilities were assumed in this model for simplicity and due to lack of available data.

Third, a lifetime horizon was considered in this model given that the goal of any gene therapy should be to serve as a lifelong therapy. However, the life of the treatment is likely to be 10-15 years due to the lack of integration of micro-Dystrophin into the muscle cells of the patients. Limiting the time horizon to 15 years results in a minor increase in QALYs and therefore the ICER of micro-Dystrophin is significantly increased. Time horizon is a major determinant of cost-effectiveness, and thus, resolving uncertainty in this parameter would increase the credibility of the model.

Fourth, adverse events were not included in the model because they have not been observed in any of the 4 patients enrolled in the ongoing phase I/IIa trial. However, this does not exclude the possibility of occurring in other patients. The most common side effect of gene therapy is an immune response against the vector used to carry the genetic material, the AAVrh74 in the case of micro-Dystrophin. The immune response can cause inflammation and in severe cases, organ failure (33).

CONCLUSION

The current model shows that the gene therapy micro-Dystrophin at a price of $1M would not reach the common cost-effectiveness threshold of $125,000 set by NICE for highly specialised technologies that deliver less than 10 QALYs to the patient during lifetime. To get a favourable recommendation for reimbursement by NICE, the price of micro-Dystrophin should be set at around $440,000.

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