Title: Developing a Natural History Model for Duchenne Muscular Dystrophy

PharmacoEconomics

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Supplementary Material 2 – Review of Natural History Models

Introduction

A review of natural history models and functional scales was performed, in order to obtain any proposed health state definitions. It was also useful to see what milestones were considered important and what clinical outcomes were used to describe the health states. A common model described in the literature was the ambulatory model – however, these states were rarely described quantitatively. As such, a secondary review was performed to identify any proposed definitions for this particular model.

Overview

The aim of this work was to identify any proposed natural history models, or functional scales, that segmented DMD into quantitatively described stages. In detail, the project was structured as follows:

1. PubMed was searched with search strings relating to DMD and to natural history on 29/08/2018.
2. Supplementary searches were performed on 11/09/2018 – 12/09/2018.
3. Search was updated on 27/09/2018 to also include the search strings “Epidemiology” OR “Epidemiological” (these were missed in error during the first round of searches).
4. Models spanning the whole disease pathway were extracted and referenced here. Functional scales were also reported, if the levels were meaningful (i.e. not just a NSAA score) and not excessive in number.

For the secondary review, PubMed was searched with search strings relating to DMD and to defining the ambulatory model on 12/09/2018. Results are extracted and referenced here.

Search methods

1.1. PubMed

- The following PubMed search methods were employed for both the main and secondary review:
    - Exclusion criteria:
        - Animal studies
        - Papers in languages other than English
- Papers not free/available to UoL
- Titles were first screened for obvious exclusion criteria.
- Abstracts were reviewed.
- If the abstract was promising, the full text was scanned, if possible, for descriptions or images of natural history models or functional scales.
- Important referenced papers were also checked.

1.2. Supplementary searches

The following supplementary searches were employed for the main review:

- NICE appraisals were reviewed for economic models on 11/09/2018.
- Google (articles and images) was searched briefly under the following strings on 11/09/2018-12/09/2018:
    - Duchenne Muscular Dystrophy natural history model
    - Duchenne Muscular Dystrophy progression model
    - Duchenne Muscular Dystrophy disease stages
    - Duchenne Muscular Dystrophy milestones

- Duchenne Muscular Dystrophy functional scale
- Duchenne Muscular Dystrophy economic model.

PubMed search strings

1.3. First PubMed search for the main review, N=259 papers

DMD string:

- "Duchenne Muscular Dystrophy" OR "DMD"

AND

Natural history string:

- "Natural history" N=148
- "Progression model" OR "Progression models" N=2
- "Disease stage" OR "Disease stages" N=25
- "Functional scale" OR "Functional scales" N=15
- "Milestone" OR "Milestones" N=37
- "Economic" N=36
- "Markov" N=4

DMD string AND any natural history strings N=259

1.4. Additional PubMed search for the main review, N=385

DMD string:

- "Duchenne Muscular Dystrophy" OR "DMD"

AND

Natural history string:

- "Epidemiology" OR "Epidemiological" N=420

All other previous natural history strings were excluded N=385

1.5. PubMed search for the secondary review, N=147

DMD string: “Duchenne Muscular Dystrophy” OR “DMD”

AND

Ambulatory string: “Ambulatory” OR Non-ambulatory”

AND

Stage string:

- “Early” OR “Late” N=50
- “Group” N=69
- “Stage” N=23
- “Status” N=47
- “State” N=18
- “Class” N=6
- “Progress” N=4
- “Transition” N=2

DMD string AND ambulatory string AND stage string N=147

Results

The searches yielded four natural history models, seven functional scales and three suggested definitions of the ambulatory model. All models/scales are included in the Appendix either graphically or as a table.

1.6. Natural history models

Landfeldt et al (1) proposed three natural history models to illustrate economic evaluations based on hypothetical data. The first model was based on a new patient-reported outcome, DMDSAT, and consisted of 24 health states plus death. Due to the volume of health states and lack of clinical meaning each health state represented, the model was not included in this report.

The second model depicted the common ambulatory model, first described in the 2010 DMD guidelines (2). This model consisted of four health states: early ambulatory, late ambulatory, early non-ambulatory and late non-ambulatory (plus death). However, no description of these health states was given in terms of clinical outcomes/functional abilities (only approximate ages for each state were given). This sparked the second review to identify potential health state definitions from the literature.

All three proposals (3-5) used the Brooke score to describe upper body function. (3, 4) used the Vignos scale to describe ambulatory function, while (5) used the ability to climb stairs and the ability to walk specifically. The general consensus was that the patients could climb stairs (varying level of assistance allowed) and walk in the early ambulatory state. Patients could no longer climb stairs in the late ambulatory state, but could still walk (varying levels of assistance of allowed). A Brooke score of 1-2 (5) or 1-3 (3, 4) defined early non-ambulatory patients, indicating that a good level of (weighted) hand-to-function was still achieved by patients. A Brooke score of greater than 2/3 defined late non-ambulatory patients, indicating that patients had poorer to no hand-to-mouth function.

The third model described by Landfeldt et al (1) was based on ventilator use only: no ventilation, night-time ventilation and day and night-time ventilation.

In PTC's recent submission to NICE for Ataluren (Translarna) (6), they described a model that consisted of five health states (plus death): ambulatory, non-ambulatory, non-ambulatory and ventilation support, non-ambulatory and scoliosis and non-ambulatory, ventilation support and scoliosis. Note that the schematic in Section 0 in an estimate of what transitions were possible as it is not clearly stated in the appraisal.

Finally, we were able to obtain GSK's draft natural history model that was being prepared for a submission to HTA bodies for Drisapersen. The model development was terminated following unsuccessful trial results. This model had a large number of states that could be collapsed into five main stages and death. The first stage was diagnosis. The second and third stages were based on the ambulatory measure the 6 Minute Walk Test (6MWT), with states representing a drop of 30m and <360m representing the third stage. The third stage was also split by the ability to stand up. The fourth and fifth stages were based on the respiratory measure Forced Vital Capacity (FVC) % predicted, with states representing a drop of 10% and <50% representing the fifth stage. The fifth stage was also split by the need for ventilation.

1.7. Functional scales

Note that the functional scales were not necessarily created to define the natural history of DMD. Scales are discussed in chronological order.

The Vignos scale (7) was developed to describe lower body function and the Brooke scale (8) to describe upper body function. Therefore, the whole disease can be described using a combination of these two measures. The Vignos scale consisted of: climbing stairs, standing from a chair, walking (including the use of leg braces), standing in leg braces, wheelchair use and being confined to bed. The Brooke scale considered full overhead reach, hand-to-mouth function (weighted and unweighted) and fine motor skills.

The adapted functional mobility scale (9), based on the scale proposed by Swinyard and Deaver (10), was used in a study investigating the relationship between bone density, mobility and fractures in patients with DMD. The scale consisted of: climbing stairs, rising from a chair, walking, standing, using a manual wheelchair and self-feeding.

Henricson et al (11) proposed a novel functional milestone scale to help demonstrate the impact of glucocorticoid therapy in DMD. The scale was based on the Timed Functional Tests (TFTs) (the ability to stand from supine, climb four stairs and walk/run 10m), the Vignos scale and the Brooke scale. The TFTs were lost in the order stated above and the Vignos scale was used to indicate the level of assistance needed in the ability to walk. A cut off of Brooke <=4 was used to split the non-ambulatory stages.

Houwen-van Opstal et al (12) proposed categories to group patients when investigating the relationship between disease severity and health related quality of life. The reduced ambulatory scale had a single ambulant state (Vignos <=6) and two non-ambulatory states; where Brooke <=3 indicated good arm abilities and Brooke >3 indicated decreased arm abilities.

Schreiber-Katz et al (13) defined a scale based on self-reported outcomes for use in a cost of illness study. The extended ambulatory scale included an extra non-ambulatory state: confinement to bed. The scale consisted of: getting up from the floor, climbing stairs, walking, (manual and electric) wheelchair use, independent standing and sitting, upper limb function and hand function. Note, that this scale was descriptive in nature.

Otto et al (14) recorded disease stage as part of a study investigating predictors of health-related quality of life. The proposed scale also extended the ambulatory model by including a pre-symptomatic state and splitting late non-ambulatory into three states. The scale consisted of: getting up from the floor, climbing stairs, walking, (electric and non-powered) wheelchair

use, standing, sitting, hand to mouth function and fine motor skills. Note, that this scale was descriptive in nature.

Lastly, the Davis Duchenne Functional scale was proposed as a means to describe the DMD pathway. Similar to Henricson et al (11), the early stages began with losing the ability to perform the TFTs in the predictable order (the ability to stand from supine was split by different time thresholds). Once the ability to walk was lost, the Brooke scale was used to describe upper body function. The milestones of interest were full overhead reach (Brooke 1), hand-to-mouth function (Brooke 2-4) and motor skills (Brooke 5), where a Brooke score of 6 represented no useful function of the hands.

Conclusion

The most commonly reported DMD natural history model is the ambulatory model with states early/late ambulatory/non-ambulatory. This is often not quantitatively defined, although proposed definitions included the ability to climb stairs and walk for ambulatory measures and the Brooke score for upper body function.

All, except one, natural history models and all functional scales considered ambulatory function. Late stage disease was described in terms of upper body function for all functional scales; in terms of scoliosis and ventilation by PTC; in terms of ventilation and FVC% predicted by GSK; in terms of type of ventilation for one Landfeldt model and in terms of non-ambulatory states with no functional definition for the other Landfeldt model.

Ambulatory function was often described by: getting up from the floor, climbing stairs and walking. The latter two abilities were either used specifically or from the Vignos scale (note that the Vignos scale was being used less as time progressed). Standing from a chair was also mentioned, but less frequently. Standing and sitting independently were also included in scale definitions quite frequently as an ability lost after the ability to walk was lost. Note, that the

6MWT was only mentioned by one model/scale and the North Star Ambulatory Assessment was not mentioned at all (probably as these measures are too recent).

Upper body function was often defined by: using a manual or electric wheelchair, having weighted hand-to-mouth function (Brooke score of 3), having unweighted hand-to-mouth function (Brooke score of 4) and having fine motor skills (Brooke score of 5). The latter three abilities were either mentioned specifically or using the Brooke scale. Having overhead reach (Brooke score of 1) and being able to touch their head (Brooke score of 2) were also mentioned, but less frequently. Note, that the Performance of Upper Limb assessment was not mentioned at all (probably as this measure is too recent).

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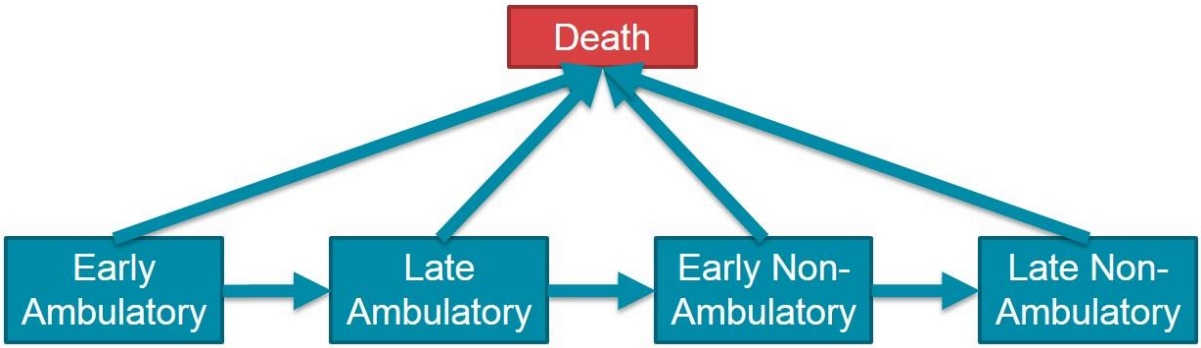
Appendix

Landfeldt (1): Ambulatory status



Spurney (3)

Stage	Status	Functional grade		Definition
		Leg	Arm	
1	Early ambulatory	1	1	Normal or slight developmental delay
2	Middle/Late ambulatory	2-6	1-2	Progression to inability to climb stairs
3	Early non-ambulatory	7	1-3	Unable to walk, able to use upper limb
4	Late non-ambulatory	7	4-6	Unable to walk, limited use of upper limb

Note: Leg = Vignos scale, Arm = Brooke scale

Heutinck (4)

Stage	Vignos	Brooke
Early ambulatory	1-3	
Late ambulatory	4-8	
Early non-ambulatory [Relative good arm function]	9-10	1-3
Late non-ambulatory [Limited arm function]	9-10	>=4

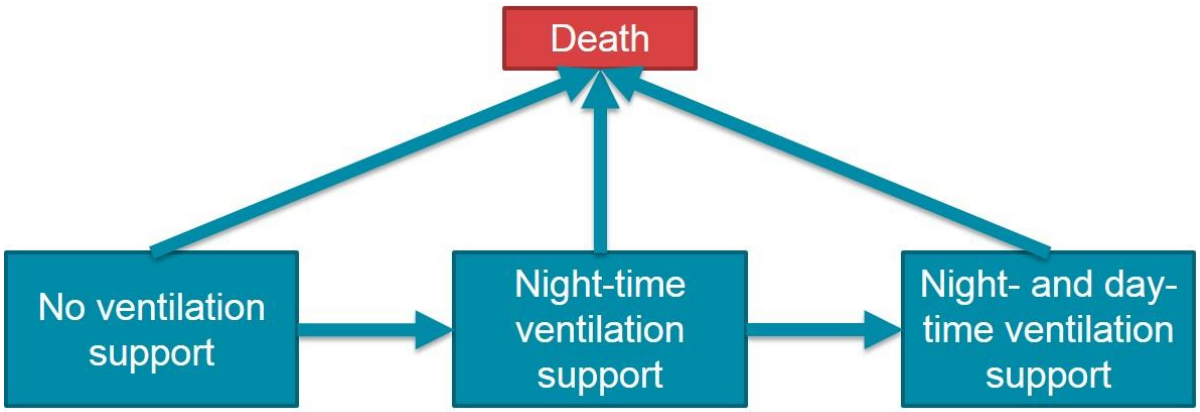
Text in publication portrayed as a table.

Janssen (5)

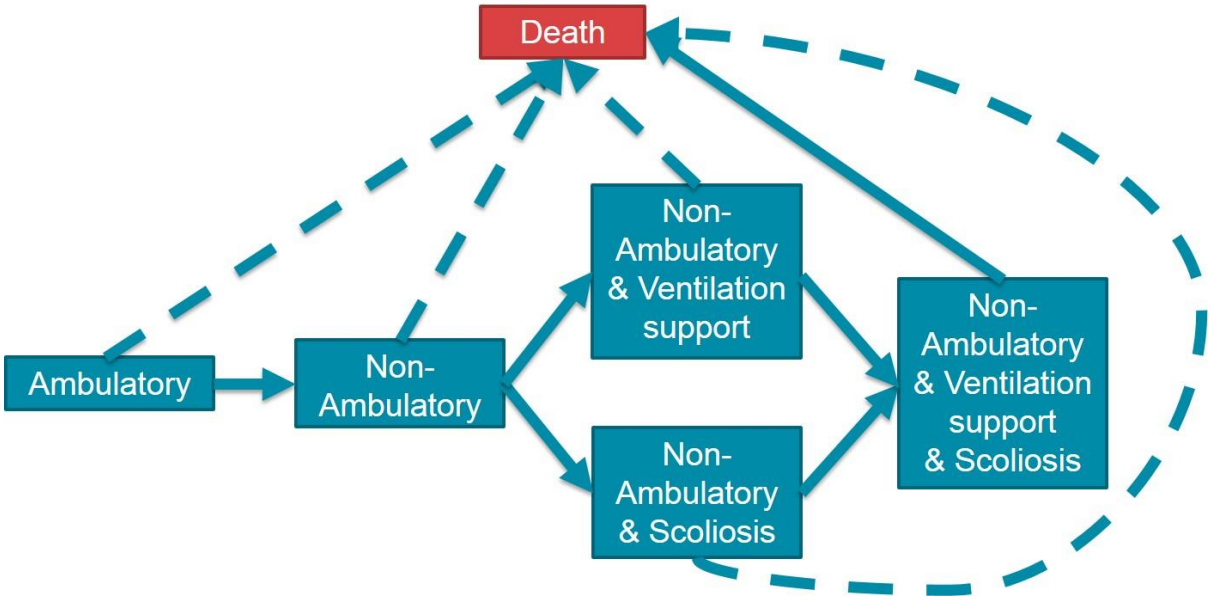
Stage	Climb stairs	Walk	Brooke
Early ambulatory	✓	✓	
Late ambulatory	✗	✓	
Early non-ambulatory			1-2
Late non-ambulatory			>=3

Text in publication portrayed as a table.

Landfeldt (1): Ventilator status



PTC Model (6)



This schematic is an estimate of what transitions were possible as it is not clearly stated in the appraisal.

Vignos (7) and Brooke (8) scales

Grade	Vignos scale for lower extremity
1	Walks and climbs stairs without assistance
2	Walks and climbs stairs with aid of railing
3	Walks and climbs stairs slowly with aid of railing (over 25 seconds for 8 standard steps)
4	Walks unassisted and rises from chair but cannot climb stairs
5	Walks unassisted but cannot rise from chair or climb stairs
6	Walks only with assistance or walks independently with long leg braces
7	Walks in long leg braces but requires assistance for balance
8	Stands in long leg braces but unable to walk even with assistance
9	Is in a wheelchair
10	Is confined to a bed

Grade	Brooke scale for upper extremity
1	Starting with arms at the sides, the patient can abduct the arms in a full circle until they touch above the head
2	Can raise arms above head only by flexing the elbow (shortening the circumference of the movement) or using accessory muscles
3	Cannot raise hands above head, but can raise an 8-oz glass of water to the mouth
4	Can raise hands to the mouth, but cannot raise an 8-oz glass of water to the mouth
5	Cannot raise hands to the mouth, but can use hands to hold a pen or pick up pennies from the table
6	Cannot raise hands to the mouth and has no useful function of hands

Larson (9): Adapted Functional Mobility Scale

Grade	Adapted Functional Mobility Scale
1	Mild abnormalities in gait. Able to climb stairs without assistance.
2	More apparent gait abnormalities. Requires a railing or other support for stairs.
3	Walks and arises from a chair independently, but cannot negotiate stairs without help.
4	Independent walking is the primary means of mobility, but a walker, braces, or other support is necessary. Unable to arise from a chair independently.
5	Primary means of mobility is a wheelchair. May stand with support for transfers. Good trunk control in the chair and able to perform all activities of daily living from the chair.
6	Wheelchair dependent and unable to stand. Needs some help propelling a manual wheelchair and with activities of daily living.
7	Unable to propel manual wheelchair. Some difficulty feeding self.
8	Unable to sit without considerable support. Requires maximal assistance for activities of daily living.

Authors adapted scale from Swinyard and Deaver (10).

Henricson (11): TFT, Brooke and Vignos

Score	Timed Functional tests			Vignos scale	Brooke scale
	Stand from supine	Climb 4 stairs	Walk/run 10m		
0	✓	✓	✓		
1		✓	✓		
2			✓	<5	
3[1]			✓	<7	
4[2]					<5
5[3]					5-6

1Cannot rise from chair (definition of Vignos <5)
2Can raise hand to mouth (definition of Brooke <5)
3Cannot raise hand to mouth (definition of Brooke >=5)
Text in publication portrayed as a table.

Houwen-van Opstal (12): Reduced ambulatory

Grade	Group	Definition
1	Ambulant	Vignos 1-6 (able to walk independently without aids)
2	Non-ambulant, good arm abilities	Brooke 1-3 (able to raise a glass of water to their mouth)
3	Non-ambulant, decreased arm abilities	Brooke 4-6

Text in publication portrayed as a table.

Schreiber-Katz (13): Extended non-ambulatory

Grade	Group	Definition
I	Early ambulatory with mild impairment	Gowers' manoeuvre, waddling gait, walking on toes, problems with climbing stairs.
II	Late ambulatory with high impairment	Walking becomes increasingly difficult, more problems climbing stairs and getting up from the floor, part-time wheelchair use.
III	Early non-ambulatory	Loss of ambulation, active manual wheelchair use possible, independent standing and sitting still possible for some time.
IV	Late non-ambulatory	Independent electric wheelchair use but decline of upper limb function and ability to sit independently.
V	Non-ambulatory with confinement to bed	Loss of independent mobility, hand function preserved on a low level.

Otto (14): Extended non-ambulatory

Grade	Group	Definition
1	Pre-symptomatic	**No symptoms**
2	Early ambulatory	**Abnormal gait**, able to climb stairs.
3	Late ambulatory	Walking more difficult, **wheelchair intermittently used**. Can still stand and sit, but losing abilities to get up from floor and climb stairs.
4	Early non-ambulatory	**Lost walking ability** but can still sit and stand. Full time active use of non-powered wheelchair which can be used independently. Arm function not or only mildly limited.
5	Non-ambulatory I	**Lost walking ability**. Active use of non-powered wheelchair not possible, because **arm strength is increasingly limited**. Hands can be raised to mouth.
6	Non-ambulatory II	Lost walking ability. Electric wheelchair necessary. **Hands cannot be raised to mouth**, but hands can be used to hold a pen or use to move electric wheelchair.
7	Non-ambulatory III	Lost walking ability. Electric wheelchair necessary. **No useful function of hands.**

Bold text was chosen by the author.

McDonald (15): Davis Duchenne Functional Milestones

Grade	Group	Definition
1	Time to stand from supine <5s	Time to stand from supine is an important prognostic factor of changes in 6-min walk distance and more generally of disease progression. A threshold value of approximately 5s differentiates between patients who are likely to show stability or improvement versus those who are likely to decline.
2	Time to stand from supine ≥5 and <10s	Patients with stand from supine values of 5s or longer are likely to experience decline in function and possibly loss of standing ability, but are not at imminent risk for loss of time to climb four stairs or ambulation.
3	Time to stand from supine ≥10s	Patients with stand from supine values of 10s or longer are at risk for losing ambulation during the next 2 years.
4	Cannot stand from supine in <30s, but can still climb four stairs	Patients with loss of stand from supine are at risk of losing ambulation over the next 2 years.
5	Cannot climb four stairs but can still complete the time to run or walk 10m test	These late ambulatory patients who have lost the ability to climb four stairs in ≤30s are at imminent risk of loss of ambulation.
6	Early non-ambulatory patients with a Brooke score of 1	These patients are at risk of losing full overhead reach as assessed by either Brooke upper extremity function rating scale or performance of upper limb measure. Brooke score of 1 indicates full overhead reach.
7	Non-ambulatory patients with a Brooke score of 2-4	This indicates a loss of full overhead reach but retained hand-to-mouth function.
8	Non-ambulatory patients with a Brooke score of 5	This indicates loss of unweighted hand-to-mouth function (but retained hand function).
9	Non-ambulatory patients with a Brooke score of 6	This indicates loss of functional use of the hands (unable to pick up objects, drive a power wheelchair hand control, or access technology with the hands).

Adapted to be portrayed in a table.

Supplementary materials 3: Rationale for each health state and definitions

Health states were chosen to satisfy the following criteria:

- A change in health state represents a change in quality of life and/or resource cost/use.
- The proposed health states make clinical sense and accurately describe DMD.
- Outcomes commonly collected in clinical trials can be mapped onto the health states.

Clinical input

Clinical opinion has been sought throughout the project to understand clinically significant milestones, to check assumptions, and to validate the proposed model:

- An initial advisory board took place on 01/11/2018 with two neurologists, one nurse, one patient advocate, and two mothers of individuals with DMD.
- Follow-up questions were discussed with two clinicians on 21/01/2019.
- The final health state proposal was circulated in March/April 2019 to twenty clinicians. Six replied (predominantly EU/UK based) with different specialisms (e.g., physiotherapist, endocrinologist).

The feedback given strongly influenced the health state definitions developed. Feedback from Duchenne UK, Project HERCULES vendors and sponsors has also been incorporated.

Clinical outcomes review

A review of outcomes in clinical trials was performed to identify which clinical outcomes were most commonly collected.

Measures of ambulatory function

The most commonly recorded ambulatory outcomes were:

- Time to stand from supine

- Six Minute Walking Test (6MWT)
- Time to walk/run 10 m
- Time to climb four stairs
- North Star Ambulatory Assessment (NSAA).

A review of best practices in collecting functional outcome data in DMD considered all of the above as commonly collected ambulatory measures.[1] The only other measure mentioned in the review was sit-to-stand.

Measures of upper body function

The most common upper body outcomes were:

- Quantitative Muscle Testing (QMT)
- Performance of Upper Limb (PUL)
- Brooke score for upper extremity.

Although QMT was the most frequent outcome reported, it can be measured in different muscles, whilst PUL and Brooke assess hand-to-mouth function.

Measures of respiratory function

The most common respiratory outcome was:

- Forced Vital Capacity (FVC).

Forced Expiratory Volume in 1 second (FEV1), Maximum Inspiratory Pressure (MIP), Peak Expiratory Flow (PEF) and Maximum Expiratory Pressure (MEP) were also quite common.

The rationale for health state definitions

Ambulatory health states

The review of clinical outcomes in trials suggested that the 6MWT, Timed Functional Tests (TFTs), and NSAA were the most commonly collected measures. Clinical opinion suggested that it was the ability to perform a functional test that was important, not the time taken, or the distance covered. The ability to stand from supine, to climb four stairs, and to walk/run 10 m were therefore selected as the key ambulatory measures to consider in the model.

The 6MWT was not selected, despite being the most prevalent primary outcome in ambulatory clinical trials. This was because it was the ability to walk that was important and this is captured by the ability to walk/run 10 m. Unlike the 6MWT, the walk/run 10 m test is routinely collected in UK clinical practice, is often used to define whether a patient is ambulatory in the clinical setting,[2] and is abundantly available in the D-RSC data.

The time to climb four stairs was also not included. This test is not routinely collected in UK practice and there can be greater variability in administration of the test in terms of step height and the techniques allowed (i.e. whether patients are allowed to hold onto rails or use their hands to get up the stairs).

Therefore, a decision was made to include stand from supine and walk/run 10 m tests in the ambulatory health state definitions. Function is lost in a predictable order: the ability to stand from supine is lost first and the ability to walk/run 10 m is lost last.[3,4] The "Early Ambulatory" state was therefore defined as being able to stand from supine and being able to walk/run 10 m. The "Late Ambulatory" state was defined as not being able to stand from supine, but still being able to walk/run 10 m.

The transfer state

There is a transitional phase after the patient has lost the ability to walk/run 10 m, where they can support their own weight to facilitate transfers, for example between wheelchair and

toilet. This ‘transfer’ stage has been included to address the significant change in resources and caregiver burden when patients exit this state.

To limit the total number of health states in the model, only one measure was used to describe the transfer state. The loss of the ability to remain standing was chosen because it was considered a more clinically significant milestone than sit-to-stand, as it is associated with a greater burden on caregivers and resource use/costs.

The transfer state was defined as no longer being able to walk/run 10 m, but still being able to stand (NSAA score of 1 or 2).

Non-ambulatory health states

It has been noted in the literature that upper limb and respiratory function provide critical information for the non-ambulant phase.[2]

Upper limb function

The review of clinical outcomes in trials suggested that QMT, PUL, and Brooke were the most commonly collected upper body measures. Clinical opinion was that QMT is measured in different muscles and is a measure of muscle strength rather than functional ability, as such, this measure was discounted for use in health state definitions.

The PUL is increasingly superseding the Brooke score. However, both measures capture hand-to-mouth function and the use of fine motor skills, and the Brooke score was the only upper body measure available in the D-RSC dataset.

Both loss of hand-to-mouth function and fine motor skills can be determined from the Brooke score. However, loss of hand-to-mouth function was chosen as the only milestone to represent upper body function for the following reasons:

- In the interest of parsimony and limiting the number of non-ambulatory states (respiratory milestones took precedence as ventilation was deemed more clinically important than upper body function).
- Hand-to-mouth function was more prevalent in the functional scales compared to fine motor skills.[3,5,6]
- Initial data exploration showed very few patients recorded a Brooke score of 6 (indicating that fine motor skills had been lost). It was expected that this was, in part, due to patients having died before reaching this milestone. Conversely, considerably more patients were expected to lose hand-to-mouth function (as this milestone is achieved first).

A Brooke score of ≤4 was used to define (unweighted) hand-to-mouth function. This was chosen over a cut off of ≤3 as it was felt this better represented the ability to self-feed and reflected the threshold suggested in the literature.[3,7]

Respiratory function

FVC was the most commonly collected respiratory measure in trials. Although other measures were also collected, data were only available for FVC in the D-RSC dataset. Race, age, and height were also collected, so these data could be converted to FVC percent predicted (FVC%).

Clinicians felt that the most important respiratory milestones were initiation of night-time and full-time ventilation, and as such, both were considered within the health state definitions.

Recent guidelines have suggested an FVC% score of <50% is an indication to begin nocturnal ventilation.[8] Unpublished work suggested that PEF (or PEF%p) may have provided a more discriminatory cut point, however, PEF data were not available in the D-RSC dataset.

No FVC or FVC% threshold has been suggested for full-time ventilation,[8] as this transition is seen as a natural progression from nocturnal ventilation. An FVC% value of <30% has frequently been associated with more severe pulmonary insufficiency and has been considered as an important milestone to reach.[9-11]

In the absence of PEF and ventilator data, the FVC% cut off value of <50% was used to indicate nocturnal ventilation and <30% was used to indicate full-time ventilation.

Order of loss of function

It was unclear whether patients would lose hand-to-mouth function or would have FVC% <50% first. As such, we allowed for either milestone to occur first in the model. We assumed that patients would only go on to have FVC% <30% after the patient has lost hand-to-mouth function and achieved FVC <50%.

Health state definitions

Table 1 provides the definition of health states in the DMD natural history model.

Table 1: Health state definitions

	Health state	Definition
1	Early Ambulatory	The patient can stand from supine and can walk/run 10 metres.
2	Late Ambulatory	The patient can no longer stand from supine but can still walk/run 10 metres.
3	Transfers	The patient can no longer walk/run 10 metres but can still (remain) standing for 3 seconds (NSAA score of 1 or 2).
4	Hand-to-mouth function No ventilator	The patient can no longer (remain) standing for 3 seconds (NSAA score of 0). The patient has hand-to-mouth (Brooke score ≤4). The patient is not on a ventilator (FVC% ≥50%).
5	No hand-to-mouth function No ventilator	The patient has no hand-to-mouth (Brooke score >4). The patient is not on a ventilator (FVC% ≥50%).
6	Hand-to-mouth function Night-time ventilation	The patient has hand-to-mouth (Brooke score ≤4). The patient is on night-time ventilation (30%≤FVC%<50%).
7	No hand-to-mouth function Night-time ventilator	The patient has no hand-to-mouth (Brooke score >4). The patient is on night-time ventilation (30%≤FVC%<50%).
8	Full-time ventilator	The patient is on full-time ventilation (FVC%<30%).
	Death	

Abbreviations: FVC%, Forced Vital Capacity percent predicted; NSAA, North Star Ambulatory Assessment.

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Supplementary materials 4: D-RSC datasets

The D-RSC data set includes both placebo-arms of trials, in which the timing of data collection is protocol-driven, and data taken from registries/routine care, where data are recorded when patients have contact with the healthcare provider. In addition to differences in the schedule of data collection, there is no standard set of variables that are routinely collected in clinical trials or registries; therefore, the metrics collected varied by dataset.

Table 2: D-RSC datasets

Study	Region	Study type	N patients	Age range (years)†	Median (IQR) follow-up	Date collected	Inclusion criteria
UC Davis	USA	Natural history	73	2–31	10.4 (7.9, 13.7)	1980s	Unknown
UC Davis 2[2,3]	USA	Test/re-test data for clinical outcome	24	4–14	7.8 (6.1, 9.4)	Publication accepted in 2009	Walk 10m, no acute illness
CCHMC[4]	USA	Clinical	97	7–16	7.4 (7.2, 7.9)	Visited 2011–2015	≥3 years follow-up
CINRG DNHS[5,6]	Argentina, Australia, Canada, India, Israel, Italy, Puerto Rico, Sweden, USA	Natural history	440	2-30	8.9 (6.2, 14.0)	Recruited 2006–2009, then again 2012–2016	No steroid-naïve, no ambulation aged 16
Santhera[7,8]	Austria, Belgium, France, Germany, Italy, Netherlands, Spain, Sweden, Switzerland, USA	Placebo arm of trial	34	10–18	14.9 (12.0, 16.0)	Recruited 2009–2012	PEF%p < 80% at baseline, no spinal surgery/ventilation
Lilly[9]	Argentina, Belgium, Canada, France, Germany, Italy, Japan, Netherlands, Russia, South Korea, Spain, Taiwan, Turkey, UK, USA	Placebo arm of trial	115	7–14	9.2 (8.0, 10.2)	Study ran 2013–2015	6MWD between 200 and 400m, left ventricular ejection fraction ≥50%
CHOP[10]	USA	Clinical	66	13-33	10.1 (7.5, 12.2)	Visited 2005–2010	English speaking

Imaging DMD[11]	USA	Natural history	100	5–18	8.0 (6.7, 9.9)	Recruitment began in 2010	Walk 100m, climb four stairs
PTC 007[12]	Australia, Belgium, Canada, France, Germany, Italy, Israel, Spain, Sweden, UK, USA	Placebo arm of trial	52	5–15	8.0 (7.0, 9.0)	Study ran 2008–2009	Walk 75m, no daytime ventilation
PTC 020[13]	Australia, Belgium, Brazil, Canada, Chile, Czech Republic, France, Germany, Israel, Italy, Poland, South Korea, Spain, Sweden, Switzerland, Turkey, UK, USA	Placebo arm of trial	115	7–15	9.0 (7.9, 10.0)	Recruited 2013–2014	Baseline 6MWD of 150m, no daytime ventilation
CINRG steroid[14]	Australia, India, Israel, USA	Clinical trial of steroids	64	4–12	7.2 (5.9, 8.4)	Study ran 2004–2007	Ambulant, muscle weakness

†Inclusion criteria ≥4 years of age as not all measures are appropriate below this age and there are limited data available.

Abbreviations: 6MWD, 6-minute walk distance; CHOP, Children's Hospital of Philadelphia CINRG DNHS, the Cooperative International Neuromuscular Research Group Duchenne Natural History Study; CCMMC, Cincinnati Children's Hospital Medical Center; DMD, Duchenne muscular dystrophy; D-RSC, Duchenne Regulatory Science Consortium; IQR, interquartile range; m, metre; PEF%p , peak expiratory flow percent predicted; PTC, PTC Therapeutics; UC Davis, University of California, Davis.

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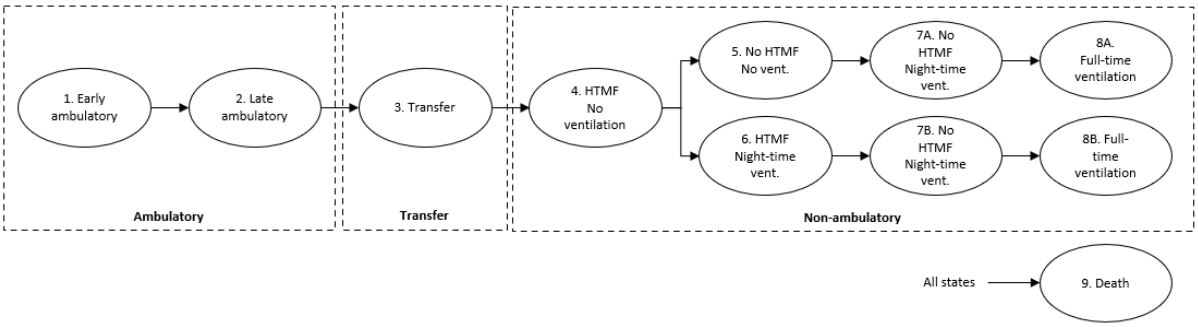
Supplementary materials 5: Elicitation exercise

Objective

Due to the paucity of data pertaining to health states 3, 4, 5, and 6 in the C-PATH data (Figure 1), an elicitation exercise was used to inform transitions into states 3, 4, and 5/6 in the natural history model.

Figure 1: Structure of the natural history model



Abbreviations: HTMF, hand to mouth function.

Methods

Data were elicited from individuals with experience of the trajectory of Duchenne muscular dystrophy (DMD), i.e., clinicians, patients, parents, and carers.

Respondents were asked the questions presented in Table 3 to obtain estimates for the age at which transitions from state 2 to 3, 3 to 4 and 4 to 5/6 were typically made. Respondents were also asked to estimate the proportions of patients that moved to state 5 from state 4 and to state 6 from state 4.

Table 3: Questions used in the elicitation exercise

Expert status	Medically Qualified
	Nurse
	Other Health Care Professional
	Parent
	Caregiver
	Patient
	Other (please specify)
Question 1	On average, at what age would you expect someone with DMD to stop being able to walk 10m (but still be able to stand, i.e., weight bearing)? [State 2 to State 3]
	Can you specify a plausible range for this average?
Question 2	Given what you have said about the average in Question 1, how long would you expect it to be before they lose the ability to stand? (or say, on average, at what age you think this would happen, if that is easier) [State 3 to State 4]
	Can you specify a plausible range for this average?
Question 3	Given what you have said in Questions 1 and 2, if someone has lost the ability to stand, but still has HTMF and does NOT require any ventilation:

	On average, how long do you think it would be before they lost either HTMF or required night-time ventilation? (or say, on average, at what age you think this would happen, if that is easier) [State 4 to State 5 or 6]
	Can you specify a plausible range for this average?
	What proportion (%) of patients do you think would lose HTMF first? [State 4 to State 5]

Abbreviations: DMD, Duchenne muscular dystrophy; HTMF, hand to mouth function.
Note: what we mean by a plausible range – lower value is such that 1 in 4 (25%) patients would be below it, and upper value is such that 1 in 4 (25%) patients would be above it.

The elicitation exercise was conducted in two phases: a pilot study and an anonymised online survey. The pilot was conducted at a Project HERCULES steering group meeting on 25/10/2019. Eight stakeholders completed at least one of the questions on the questionnaire.

The subsequent anonymised online survey was circulated by Duchenne UK and received 20 responses. Respondents were all from the UK and included:

- Two “medically qualified”
- Twelve “parent”
- Two “parent and carer”
- One “parent and nurse”
- Three “patient”.

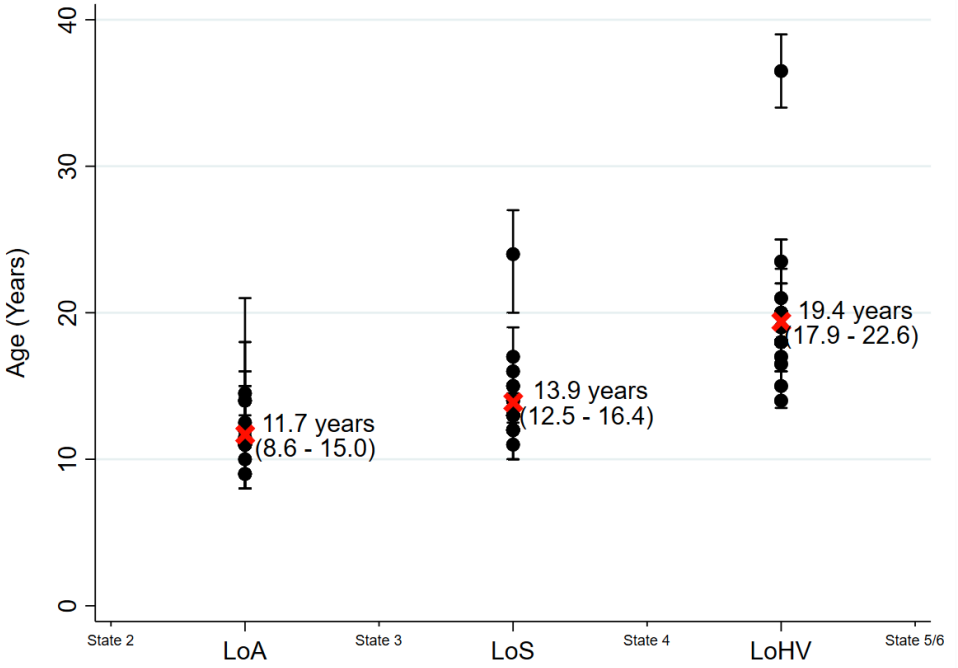
For both the pilot study and subsequent online survey, fifty hypothetical patients were generated in state 3 with starting ages simulated from a normal distribution, with the mean equal to the mean age of answers to Question 1, and standard deviation selected such that 50% of the normal distribution covered the mean age range of answers in Question 1. Their transition times to state 4 were simulated by taking their age in state 3 and adding a random value from a normal distribution with the mean equal to the mean difference between Question 1 and Question 2, and a standard deviation selected in the same way as for state 3. This value was left-truncated at 0.1 years and right-truncated at 15 years. This was repeated for transitions from state 4 to states 5/6 with these transitions apportioned to state 5 and state 6 based on responses to the final part of Q3.

Results

The results of the online elicitation exercise (

Figure 2) were broadly similar to the pilot elicitation of eight stakeholders. The mean age at each transition, and mean age range, are shown next to each individual response.

Figure 2: Elicitation data from 20 respondents on DMD progression (online survey)



Abbreviations: DMD, Duchenne muscular dystrophy; LoA, loss of ambulation (10 m); LoHV, loss of hand to mouth function/requires night ventilation; LoS, loss of standing (weight-bearing).

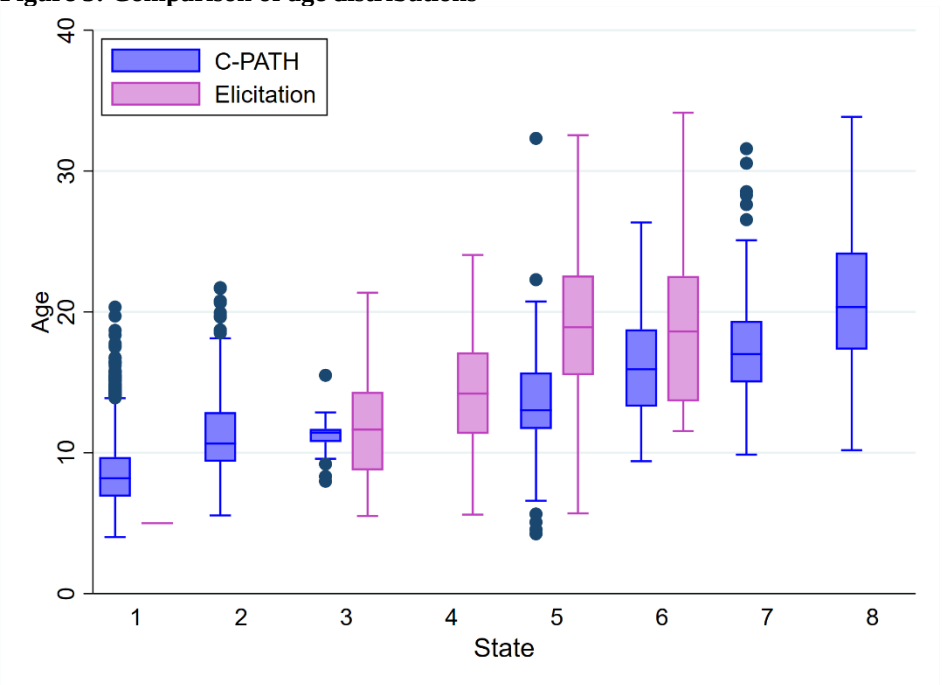
The loss of ambulation (state 2 to 3) was estimated by both groups to occur at around 12 years, and the loss of hand to mouth function or requirement of night-time ventilation (state 4 to state 5/6) was estimated to occur around 6 years after losing the ability to stand. The results from the online survey predicted a slightly shorter stay in state 3, estimating that patients lose the ability to stand at around 14 years. The ages at loss of ambulation were simulated from a normal (11.7, 5) distribution, at loss of standing from a normal (age_{LOA}+2.2, 2) and at loss of hand to mouth function/requiring night ventilation from a normal (age_{LOS}+5.5, 3) to reflect the mean ages and age ranges.

On average, respondents estimated that 52.1% of patients move from state 4 to state 5, with a minimum of 20% and a maximum of 80%. As such, 50% of patients were assigned to state 5 from state 4 and 50% to state 6 from state 4 in the simulated dataset.

Congruence of age distributions with those from the D-RSC data set

A comparison of age distributions for the base case simulated dataset from the online elicitation exercise and the C-PATH dataset are shown in **Figure 3**.

Figure 3: Comparison of age distributions



The mean (and SD of) ages in states 3, 4, 5, and 6 respectively of patients from the simulated dataset are 11.8 (4.2), 14.3 (4.5), 19.5 (5.6), and 19.3 (6.4), respectively. There is some small difference in the age distributions in state 5 between the two datasets. This is largely due to the small numbers in the simulated dataset, since only 30 simulated patients were assigned to state 5. Otherwise, overall there is largely agreement between the age distributions.

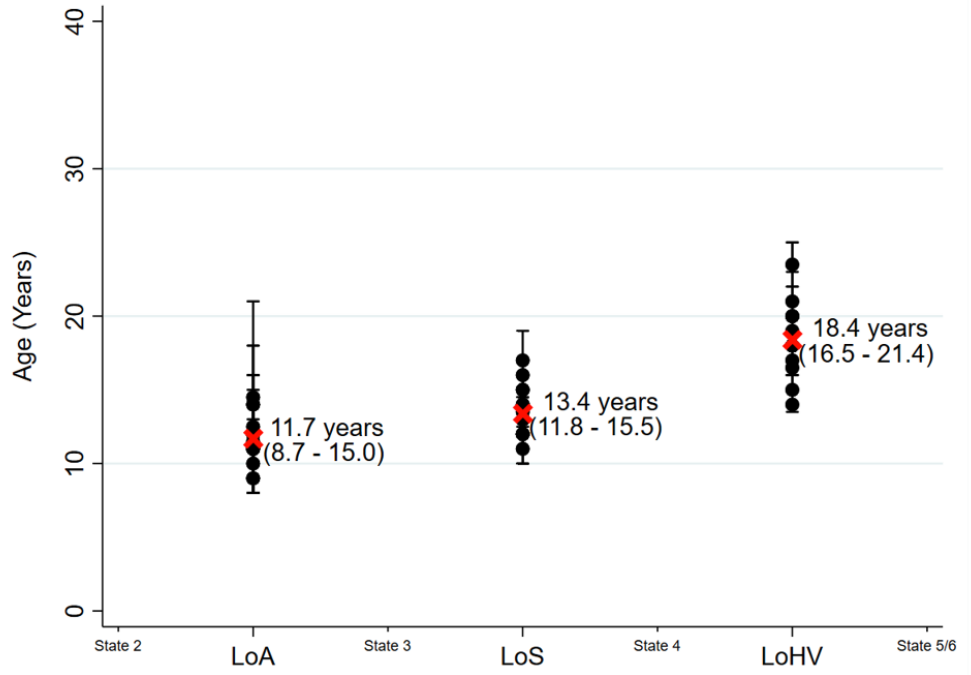
Sensitivity analyses

A number of sensitivity analyses were conducted. These included the exclusion of an outlying survey response, and varying the methods used to generate the age distribution in each state.

There was one outlying response in the online survey. Excluding this response from the analysis showed that the outlying response did little to change the overall results (

Figure 4).

Figure 4: Sensitivity analysis removing the one outlying response in the online survey (n=19)



Abbreviations: LoA, loss of ambulation (10 m); LoHV, loss of hand to mouth function/requires night ventilation; LoS, loss of standing (weight-bearing).

The dataset was re-simulated multiple times with different parameter values for the age distributions chosen to assess the sensitivity of the model to the elicitation exercise. These are detailed below in Table 2.

Table 2: Different scenarios considered in the sensitivity analysis

Scenario	Sample Size	Values for Normal Distributions	Proportion
Base case	50	N(11.7, 5), N(age_{LOA}+2.2, 2), N(age_{LOS}+5.5, 3)	50%

Other values	20	N(11.7, 2), N(age_{LOA}+2.2, 1), N(age_{LOS}+5.5, 1)	25%
	100	N(10.7, 5), N(age_{LOA}+2.2, 2), N(age_{LOS}+5.5, 3)	75%

Abbreviations: LoA, loss of ambulation (10 m); LoS, loss of standing (weight-bearing).

The sample size was varied to assess the impact of the weight that the simulated dataset was providing. The values for the normal distributions of ages in each state and the proportion moving from state 4 to state 5 were varied to quantify the uncertainty around the elicitation responses. Each time a different dataset was simulated, the model was re-estimated and gave very similar results in terms of transition intensities and probabilities. The other simulated datasets from the sensitivity analysis also showed similar agreement with the age distributions in the C-PATH dataset.

Conclusions

In the absence of clinical/real-world data, the elicitation exercise is considered to represent an appropriate alternative [1].

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Supplementary materials 6: Transition intensity matrices

Due to uncertainty in the transitions into and out of state 3 (transfer), where data were obtained via the elicitation exercise, the NHM was generated including the transfer state (Model A) and without (Model B).

Table 4: Transition intensity matrix – Model A

											Death	
State	**1**	**2**	**3**	**4**	**5**	**7A**	**8A**	**6**	**7B**	**8B**	**9 (<30 years)**	**9 (≥30 years)**
1	0	0.163989	0	0	0	0	0	0	0	0	8.00E-05	8.00E-05
2	0	0	0.289386	0	0	0	0	0	0	0	0.00127	0.00127
3	0	0	0	0.650225	0	0	0	0	0	0	0.00113	0.00113
4	0	0	0	0	0.2914	0	0	0.280192	0	0	0.00658	0.00658
5	0	0	0	0	0	0.19836	0	0	0	0	0.01345	0.01345
7A	0	0	0	0	0	0	0.402481	0	0	0	0.03092	0.03092
8A	0	0	0	0	0	0	0	0	0	0	0.03913	0.07864
6	0	0	0	0	0	0	0	0	0.183241	0	0.02943	0.02943
7B	0	0	0	0	0	0	0	0	0	0.504425	0.03691	0.03691
8B	0	0	0	0	0	0	0	0	0	0	0.03864	0.07766
9	0	0	0	0	0	0	0	0	0	0	0	0

Table 5:Transition intensity matrix – Model B

State	1	2	4	5	7A	8A	6	7B	8B	Death	
										9 (<30 years)	9 (≥30 years)
1	0	0.155304	0	0	0	0	0	0	0	0.00018	0.00018
2	0	0	0.235629	0	0	0	0	0	0	0.00244	0.00244
4	0	0	0	0.219	0	0	0.21058	0	0	0.00744	0.00744
5	0	0	0	0	0.2059	0	0	0	0	0.01539	0.01539
7A	0	0	0	0	0	0.40027	0	0	0	0.03403	0.03403
8A	0	0	0	0	0	0	0	0	0	0.03856	0.0775
6	0	0	0	0	0	0	0	0.185059	0	0.0298	0.0298
7B	0	0	0	0	0	0	0	0	0.501561	0.03479	0.03479
8B	0	0	0	0	0	0	0	0	0	0.03857	0.07752
9	0	0.155304	0	0	0	0	0	0	0	0.00018	0.00018

Supplementary materials 7: Mean (95% CI) time in state

Table 6: Mean time in states for different populations of DMD patients

State >		1	2	3	4	5	7A	8A	6	7B	8B
Whole population	Mean	6.09	3.44	1.54	1.73	4.72	2.31	12.72	4.70	1.85	12.88
	CI	(5.3, 7.0)	(2.8, 4.2)	(1.1, 2.1)	(1.3, 2.3)	(3.4, 6.5)	(1.7, 3.2)	–	(3.5, 6.3)	(1.3, 2.5)	–
Steroid users	Mean	5.68	3.46	1.61	1.71	5.61	2.13	12.72	5.53	1.93	12.88
	CI	(5.0, 6.5)	(2.8, 4.3)	(1.2, 2.2)	(1.3, 2.3)	(3.9, 8.0)	(1.5, 3.1)	–	(4.0, 7.6)	(1.3, 2.8)	–
Mutation= 0‡	Mean	5.78	3.40	1.69	1.90	4.57	2.16	12.72	4.86	2.03	12.88
	CI	(5.0, 6.7)	(2.7, 4.2)	(1.3, 2.3)	(1.4, 2.5)	(3.3, 6.4)	(1.5, 3.0)	–	(3.5, 6.7)	(1.4, 2.9)	–
Mutation = 1¶	Mean	5.00	1.73	3.23	2.48	26.06	6.08	12.74	10.74	0.64	12.90
	CI	(4.8, 6.1)	(1.2, 2.6)	(2.3, 4.5)	(1.8, 3.4)	(12.4, 54.7)	(1.2, 30.3)	–	(6.1, 18.8)	(0.2, 1.9)	–

Abbreviations: CI, confidence interval.

‡ Dup, Skip 51, Skip 53, Small mutation, Stop, Any other deletion.

¶ Del 3-7, Skip 44, Skip 45.

Table 7: Mean time in states for all sensitivity analyses

State >		1	2	3	4	5	7A	8A	6	7B	8B
Model B‡	Mean	6.43	4.20	NA	2.29	4.52	2.30	12.90	4.65	1.86	12.90
	CI	(5.6, 7.4)	(3.4, 5.2)	NA	(1.7, 3.1)	(3.3, 6.2)	(1.7, 3.2)	-	(3.5, 6.2)	(1.3, 2.6)	-
All mortality rates¶	Mean	6.09	3.43	1.53	1.73	4.43	2.18	8.35	4.19	1.76	8.74
	CI	(5.3, 7.0)	(2.8, 4.2)	(1.1, 2.1)	(1.3, 2.3)	(3.3, 6.0)	(1.6, 3.0)	-	(3.2, 5.4)	(1.3, 2.4)	-
N§ = 20	Mean	6.60	4.03	0.89	1.06	2.84	2.33	12.71	4.50	1.85	12.87
	CI	(5.7, 7.6)	(3.2, 5.1)	(0.6, 1.4)	(0.7, 1.7)	(2.1, 3.9)	(1.7, 3.2)	-	(3.4, 6.0)	(1.3, 2.6)	-
N§= 100	Mean	5.56	3.01	2.06	2.15	6.86	2.30	12.72	6.54	1.84	12.87
	CI	(5.0, 6.3)	(2.5, 3.6)	(1.6, 2.6)	(1.7, 2.7)	(5.1, 9.3)	(1.7, 3.2)	-	(5.0, 8.6)	(1.3, 2.5)	-
25% pts 4>5††	Mean	6.09	3.44	1.54	1.71	2.94	2.32	12.72	6.15	1.84	12.88
	CI	(5.3, 7.0)	(2.8, 4.2)	(1.2, 2.1)	(1.3, 2.3)	(2.1, 4.1)	(1.7, 3.2)	-	(4.7, 8.1)	(1.3, 2.5)	-
75% pts 4>5††	Mean	6.09	3.44	1.54	1.71	5.41	2.30	12.72	4.13	1.85	12.88
	CI	(5.3, 7.0)	(2.8, 4.2)	(1.2, 2.1)	(1.3, 2.3)	(3.9, 7.4)	(1.7, 3.2)	-	(3.1, 5.6)	(1.3, 2.6)	-
Lower SD	Mean	6.03	3.44	1.54	1.83	4.69	2.31	12.71	4.67	1.85	12.87
	CI	(5.3, 6.9)	(2.8, 4.2)	(1.2, 2.0)	(1.4, 2.4)	(3.4, 6.5)	(1.7, 3.2)	-	(3.5, 6.3)	(1.3, 2.5)	-
Mean age per state -1y‡‡	Mean	5.99	3.30	1.42	1.77	4.70	2.31	12.72	4.69	1.85	12.88
	CI	(5.2, 6.9)	(2.7, 4.0)	(1.1, 1.9)	(1.3, 2.4)	(3.4, 6.5)	(1.7, 3.2)	-	(3.5, 6.3)	(1.3, 2.5)	-
Mean age per state +1y‡‡	Mean	6.20	3.58	1.64	1.70	4.74	2.31	12.72	4.71	1.85	12.88
	CI	(5.4, 7.1)	(2.9, 4.4)	(1.2, 2.2)	(1.3, 2.3)	(3.4, 6.5)	(1.7, 3.2)	-	(3.5, 6.3)	(1.3, 2.5)	-

‡Model B excludes the transfer state (state 3).

¶Including mortality data pre- and post-1990 identified in the targeted literature review.

§Varying the number of patients simulated in the pseudo IPD, where n=50 in the base-case analysis.
††Varying the proportion of patients that move from state 4 to 5 (50% in the base-case analysis), where the remainder of patients are assumed to move from state 4 to 6.
‡‡Varying the mean age in each state by ±1 year.