Considerations for modelling caregiver spillover within economic evaluations for neurological disorders: Spinal muscular atrophy (SMA), Duchenne muscular dystrophy (DMD) and multiple sclerosis (MS)

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Background

- There is a growing consensus among Health Technology Assessment (HTA) bodies to formally account for the societal impact of disease (e.g. Health Economics Methods Advisory [HEMA][1]), including the burden of informal care on caregivers.
- Certain methods guidelines do include recommendations on the implementation of societal elements. For example:

National Institute for Health and Care Excellence (NICE):[2]

"The perspective on outcomes should be all relevant health effects, whether for patients or, when relevant, other people (mainly carers)."

Canada's Drug Agency – Agence des médicaments du Canada (CDA-AMC):[3]

"If there are additional outcomes of interest for a broader perspective beyond the decision problem, these could be considered in a scenario analysis or discussed."

Zorginstituut Nederland (ZIN):[4]

"The quality of life of informal caregivers must be included in a scenario analysis when relevant."

Institute for Clinical and Economic Review (ICER):[5]

"...each analysis should include an analysis using a modified societal perspective, which will include costs and outcomes beyond direct health care impacts."

- However, there remains a lack of guidance on the technical implementation of societal value elements in health economic models resulting in a lack of consistency across evaluation. Structural assumptions within health economic models can have a substantial impact on the cumulative quality-adjusted life years (QALYs) accrued by caregivers.
- Additionally, there is a lack of consensus on instruments that are valid and sensitive to capture meaningful changes in caregiver health-related quality of life (HRQoL).
- Inconsistent HTA methodologies create uncertainty in long-term and marginal impacts of caregiver HRQoL, which may also impact decision-making influenced by the societal perspective, contributing to an inefficient allocation of resources.

Objective

- Despite consensus to capture the impact of informal care within economic evaluation,[6,7] little is known about how caregiver HRQoL is incorporated in cost-effectiveness analyses.
- Here, analyses are presented for capturing caregiver HRQoLs in three neurological disorders; spinal muscular atrophy (SMA), Duchenne muscular dystrophy (DMD) and multiple sclerosis (MS).

Methods

- This study used natural history data in economic models developed for neurological disorders to quantify the impact of incorporating different strategies for caregiver HRQoL on the total QALYs.
- Analyses were conducted from both the UK National Health Service (NHS) and societal perspectives.
- Unlike patient HRQoL where only the absolute health state utility values (HSUVs) were used throughout the analyses, two primary methods were applied to incorporate caregiver HRQoL into the economic models. The absolute utility approach and the disutility approach.
- Each approach was evaluated through scenario analyses as described below:

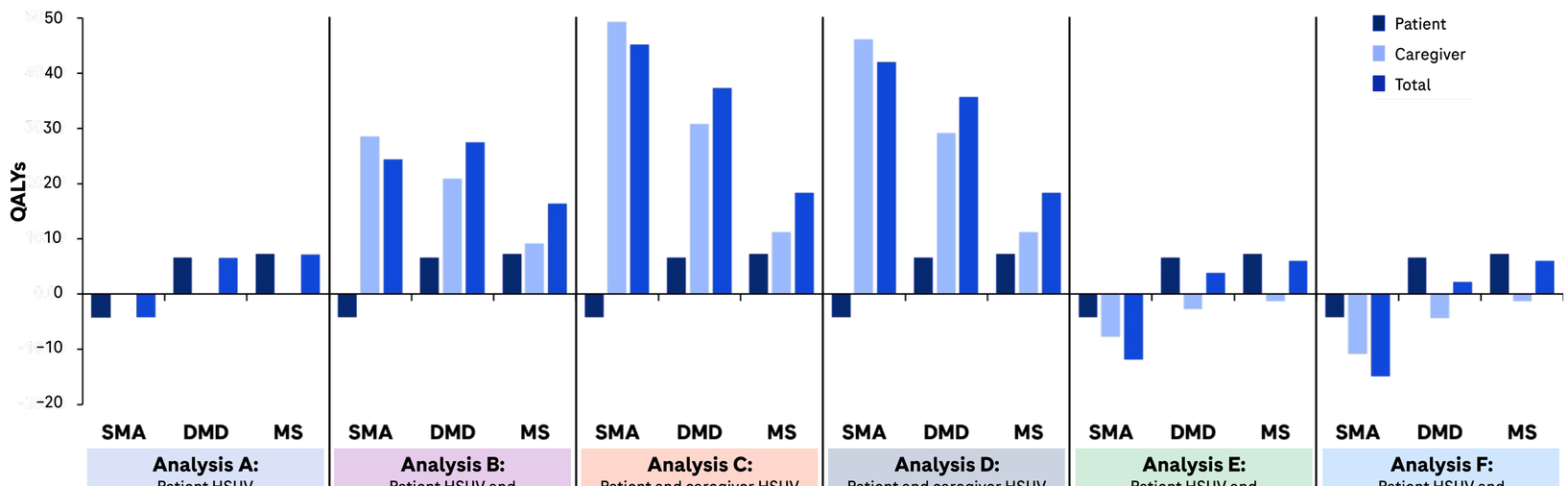
Reference Case – UK NHS	
A	Reference Case – UK NHS Only patient HSUVs were included; caregiver HRQoL was excluded.
Absolute utility approach	
Absolute HSUVs were assigned to caregivers (i.e. family QALYs) over the patient's lifetime. Following the patient's death, caregiver HRQoL was modelled based on two assumptions:	
B	Caregiver HRQoL was excluded from the analysis (i.e. set to zero) following the patient's death.
C	Caregiver HRQoL reverted to age- and sex-matched general population norms after the patient's death.
Absolute utility and disutility approaches	
D	Differed from analysis C only in the fact that it accounts for bereavement-related disutility* after the patient's death.
Disutility approach	
Caregiver HRQoL was captured using the disutility approach over the patient's lifetime. Following patient death, caregiver HRQoL was modelled based on the following two assumptions:	
E	Caregiver HRQoL was excluded from the analysis post-patient death.
F	A bereavement-related disutility was applied as a stand-alone input in the bereaved state.

- The duration of bereavement-related disutility varied depending on the disease. In SMA and DMD models (**Supplementary Figures 1a and 1b**), the burden of bereavement on caregiver HRQoL was assumed to gradually decrease over the caregiver's remaining lifetime.[8]
- In MS (**Supplementary Figure 1c**), bereavement disutility was applied for a fixed duration of 1 year following patient death.[9]
- Model parameters (e.g. time horizon, discount rate, number and age of caregivers), and structural assumptions were aligned with established best practices guidelines. An overview of the modelling is shown in **Supplementary Table 1**.
- All data sources and parameter inputs (**Supplementary Tables 2 and 3**) were explicitly cited.

*Defined as the reduction in a caregiver's HRQoL following the patient's death.

Results

Figure 1. Patient and caregiver lifetime QALYs from natural history data across the analyses and disease areas



QALYs	SMA	DMD	MS	SMA	DMD	MS	SMA	DMD	MS	SMA	DMD	MS	SMA	DMD	MS	SMA	DMD	MS
	Analysis A: Patient HSUV			**Analysis B:** Patient HSUV and caregiver HSUV (excluding post-patient death)			**Analysis C:** Patient and caregiver HSUV (including post-patient death: General population utility)			**Analysis D:** Patient and caregiver HSUV (including post-patient death: General population utility and bereavement disutility)			**Analysis E:** Patient HSUV and caregiver disutility (excluding post-patient death)			**Analysis F:** Patient HSUV and caregiver disutility (including post-patient death: Bereavement disutility)		
Patient	−4.15	6.54	7.18	−4.15	6.54	7.18	−4.15	6.54	7.18	−4.15	6.54	7.18	−4.15	6.54	7.18	−4.15	6.54	7.18
Caregiver	0	0	0	28.51	20.89	9.15	49.28	30.80	11.21	46.18	29.16	11.21	−7.67	−2.72	−1.21	−10.77	−4.35	−1.21
Total	−4.15	6.54	7.18	24.36	27.44	16.33	45.13	37.34	18.39	42.03	35.70	18.39	−11.82	3.82	5.97	−14.92	2.19	5.97

A	• Caregiver HRQoL was not included in the reference case; only patient HSUV was incorporated, which was low due to disease morbidity in untreated patients.
B	• The total QALYs were substantially higher than in analysis A. • Caregiver QALYs contributed 87.29%, 76.13% and 56.03% of the total QALYs in the SMA, DMD and MS models, respectively.
C	• The total QALYs further increased, which assumed that caregiver HRQoL reverted to the same as the general population following the patient's death. • This led to the caregiver QALY contribution rising to 92.23% for SMA, 82.49% for DMD, and 60.96% for MS. • The comparatively small contribution to the total QALYs of natural history patients indicates the severity of the three neurological conditions considered in this study.
D	• This analysis differed from analysis C only in the approach used to model post-patient death, with the bereavement disutility applied following patient death. • The inclusion of bereavement disutility in analysis D marginally impacted the total QALYs compared with analysis C across all three conditions, with caregiver contributions declining from 92.23% to 91.75% in SMA and from 82.49% to 81.68% in DMD, with no observed difference for MS.
E	• Caregiver spillover effects were modelled as disutility, resulting in an overall reduction in total QALYs that reflects HRQoL burden associated with caregiving. – For SMA, the impact of caregiving was substantial as the combined patient and caregiver total QALYs further decreased to −11.82 compared with the UK NHS reference case, with caregiver QALYs accounting for 64.89% of the total QALYs. • The reduction in total QALYs was less pronounced, though still substantial, in the DMD and MS models. – For DMD, the total QALYs decreased to 3.82, with caregiver QALYs accounting for 29.37% of the total QALYs. – For MS, the resulting total QALYs were 5.97, with caregiver QALYs contributing 14.42% of the total QALYs.
F	• Similar to analysis E, the total QALYs for SMA further decreased to −14.92 in analysis F compared with the reference case, with caregiver QALYs accounting for 72.18% of the total QALYs. • For DMD, the total QALYs decreased to 2.19, with caregiver QALYs accounting for 39.94% of the total QALYs. • There was no observable difference in total QALYs between analyses E and F for MS.

Discussion

- Our approaches align with current recommendations and suggestions for caregiver spillover modelling; inclusion in models is feasible although the required parameters and adjustments to models should be considered.
- As expected, including caregiver HRQoL using the absolute utility framework substantially increased the total QALYs.
- Presenting disaggregated results by modelling approach helps demonstrate the long-term impact on HRQoL of caregivers in the absence of treatment for these three neurological disorders.
- Parameterisation of model inputs is important and should be done consistently, paying attention to uncertainties.
- Whilst previous recommendations have already suggested the importance of potential disease duration and intensity,[10,11] attention should be given to the relationship and age of caregivers and the patient family member they are caring for (**Supplementary Figure 2**).
- Sometimes caring brings improvements in utility but it also increases daily care burden and bereavement.

Limitations

- Feasibility of the models:
  - Current recommendations encourage the use of the same utility instrument for both patients and caregivers when aggregating their QALYs; whilst mapping algorithms exist for some instruments, this approach is not always feasible and introduces further bias.
  - Additional data/evidence are needed to improve modelling approaches: Robust and locally relevant parameterisation of patient and caregiver utilities, as well as information on age, sex and other confounding factors to HRQoL, plus other process utilities/disutilities for caregivers when comparing treatments.
  - Not all countries have general population algorithms available.
- Upskilling of knowledge of caregiver health spillovers is needed.
- There may be shifts in caregiving over time that could impact results; the duration of caring may be impacted by caregiver age and the number of caregivers.
- Normalising utility values to the general population is not always possible.

Conclusions

When modelling caregiver health spillovers across neurology, current recommendations are useful but vague and open to interpretation, with micro-parameters and assumptions left to the discretion of the modeller.

- The total QALYs in each of the neurological disorders differed depending on the modelling approach:
  - QALYs ranged from −14.92 to 45.13 in SMA; from 2.19 to 35.70 in DMD; and from 5.97 to 18.39 in MS.

Modellers implementing caregiver health spillovers should:

- **Be transparent about structural assumptions** (e.g. modelling post-mortem, adjustments to general population utilities or disease related utilities).
- **Report caregiver evidence sources**
  - Caregiver data: the mean age of the caregiver at the initiation of caregiving, survival rates, number of caregivers allocated to each patient health state, the proportion of patients receiving informal care, bereavement (general or disease specific), duration of bereavement, duration of care, etc.
  - The source and approach used to collect caregiver HRQoL data (i.e. discrete choice experiment and time trade-off).
- **Be aware of and adjust for disease areas nuances:**
  - Chronic versus acute disease, age of disease onset for patient, and pay attention to the patient–caregiver relationship and its impact on inputs (i.e. parameters) and outputs (i.e. QALYs) over time.

HTA bodies should be aware of the potential variation in caregiver QALYs in results driven by parameterisation and modelling assumptions, as well as the underlying impacts on caregivers common to particular disease areas and patient–caregiver relationships.

Abbreviations

CADTH, Canadian Agency for Drugs and Technologies in Health; CDA-AMC, Canada's Drug Agency – Agence des médicaments du Canada; DMD, Duchenne muscular dystrophy; HEMA, Health Economics Methods Advisory; HRQoL, health-related quality of life; HSUV, health state utility value; HTA, Health Technology Assessment; ICER, Institute for Clinical and Economic Review; MS, multiple sclerosis; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; OHE, Office of Health Economics; QALY, quality-adjusted life year; SMA, spinal muscular atrophy; ZIN, Zorginstituut Nederland.

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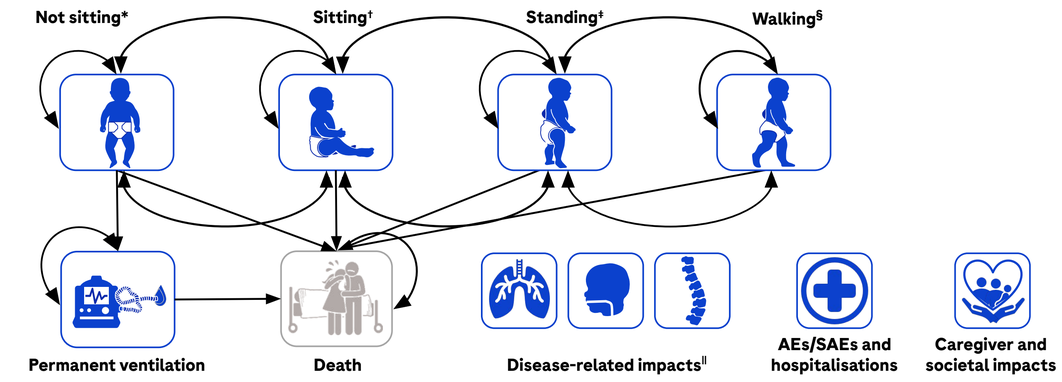
Supplementary material

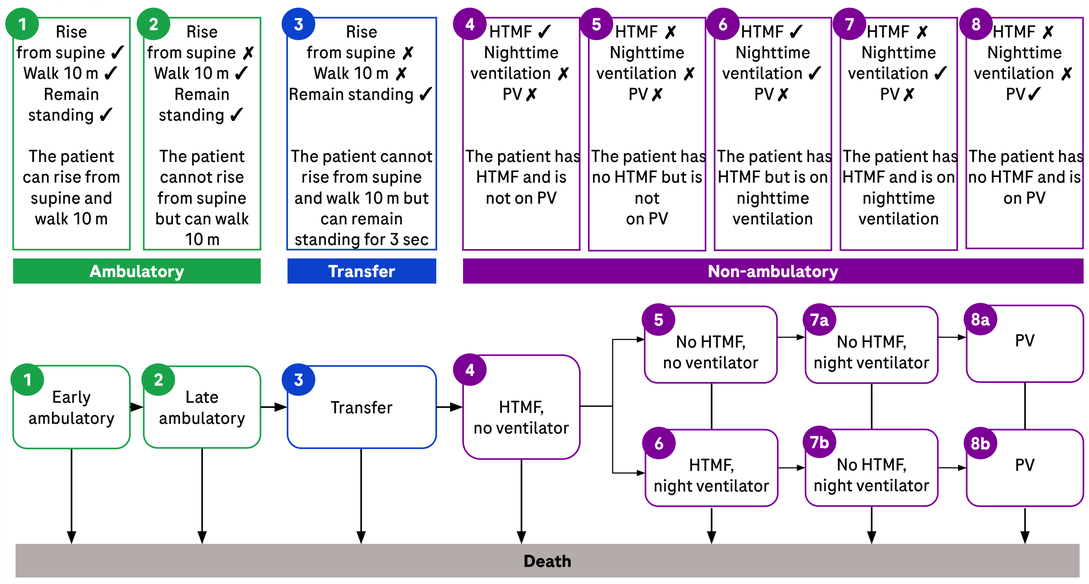
Figure 1. Model structures in neurological disorders

A. Presymptomatic SMA

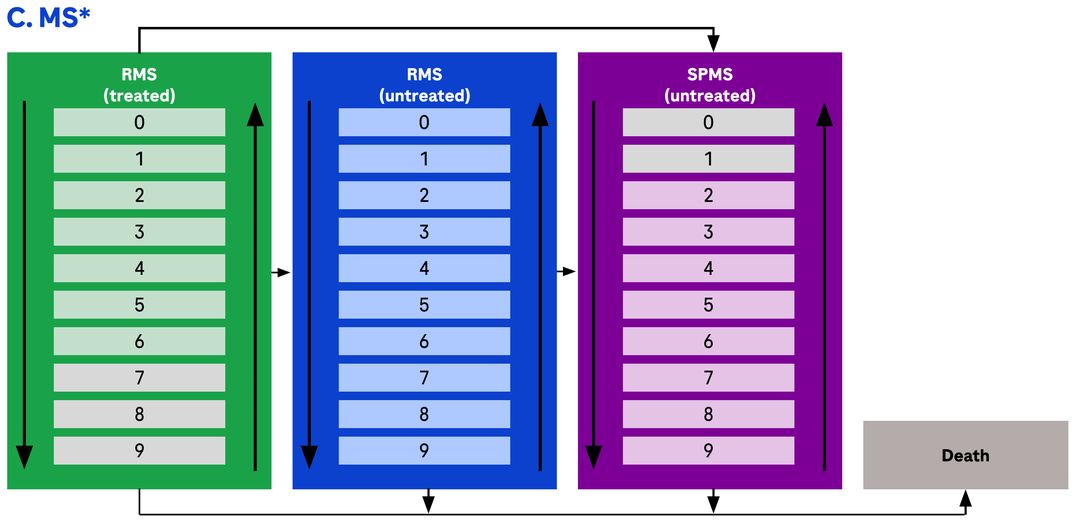


*Neither sitting, standing or walking. †Supported: sits with support at hips (1), props self up (2); unsupported: stable sitting (3), pivots and rotates (4). ‡Supported: stands with support (2); unsupported: stands unaided (3). §Supported: cruising (2); unsupported: walking independently (3). ‖Includes respiratory support, scoliosis and bulbar function.
All milestones assessed with Hammersmith Infant Neurological Examination, Module 2.

B. DMD



C. MS*



*Scores on the Expanded Disability Status Scale (EDSS) range from 0 to 10 (0 indicating full functional ability and 10 indicating death).

Figure 2. Potential trends between patient and caregiver age and the patient–caregiver relationship[1,2]

Caregiver age \ Patient age	Child (0–18)	Adult (young) (19–35)	Adult (mid) (36–64)	Adult (senior) (65–100)
Adult (young) (19–35)	DMD *e.g. parent caring for child*	–	–	–
Adult (mid) (36–64)	SMA *e.g. parent caring for child*	–	MS *e.g. spouse caring for spouse; parent caring for adult child*	MS *e.g. adult child caring for elderly parent*
Adult (senior) 65–100	–	–	–	–

Table 1. Modelling overview

Section/topic*	SMA	DMD	MS
Patient population	Presymptomatic SMA, genetically diagnosed with 2–4 *SMN2* copies	Ambulatory boys 4–7 years old	Relapsing-remitting MS, Adults (mean 37-years-old)
Mean patient age	20 days[3]	6 years[4]	37 years[5]
Patient disease progression and survival	Pediatric Neuromuscular Clinical Research Network study[6]	Duchenne Regulatory Science Consortium[7] Broomfield et al. 2021[8]	Palace et al 2014[9] Pokorski et al 1997[10] Office for National Statistics[11]
Time horizon	85 years (lifetime)	70 years (lifetime)	63 (lifetime)
Perspectives	HS Payer, Societal†		
Discount rate	1.5%[12]	3.5%[12]	3.5%[12]
Geographical location	UK	UK	UK
Model structure and software, validation	Markov model in Microsoft Excel® 5 health states related to gross motor function and death, proportional disease-related impacts modelled as time to event; half-cycle corrected	Markov model in Microsoft Excel® 9 health states defined by ambulatory status, cardiac and respiratory functionality; half-cycle corrected	Markov model in Microsoft Excel® 21 health states defined by EDSS disability scales, including treatment discontinuation and transitions from relapsing MS (RMS) to secondary progressive MS (SPMS). Relapses modelled as events with rates varied by EDSS; half-cycle corrected
Patient utilities	TA755 report[13]	Landfeldt et al. 2017[14] (HUI-3)	Orme et al. 2007[15] (EQ-5D-3L)
Modelling outcomes (HRQoL)	QALYs for both patients and caregivers†	QALYs for both patients and caregivers†	QALYs for both patients and caregivers†
Approach to engagement with patients and others affected by the study	External experts (neurologists, physiotherapists) consulted during the development of SMA models, PAGs were included as well. SMA models have been reviewed by several global HTA bodies, some examples include: CDA-AMC,[16] INESSS,[17] HAS,[18] NCPE,[19] NICE,[12] PBS,[20] SMC,[21] TLV[22] and ZiN[23]	Project HERCULES (multi-stakeholder collaboration between pharmaceutical companies, clinicians, academics, patients organisations, HTA bodies)[24]	Reviewed by several HTA bodies including: NICE,[25] CADTH,[26] HAS[27] and INESSS[28]

*Selected items derived from the CHEERS checklist.[29] †Societal (caregiver health spillover) parameters described in Table 2.

Table 2. Key input parameters for caregiver health spillover

	SMA	DMD	MS
Number of caregivers	2*	Ambulatory phase :1 Non-ambulatory phase: 2	1[30]
Caregiver assessment	EQ-5D-3L	EQ-5D-3L	EQ-5D[30]
Caregiver utility source (i.e. literature or direct elicitation)	Rowell et al. 2020[31]	Landfeldt et al. 2017[14]	Acaster et al. 2013[30]
Caregiver utility tariffs (country)	UK (HSE 2024)[32]	UK (HSE 2014)[32]	UK (Dolan et al. 1997)[34]
Caregiver mean age at baseline	35†	29†	51[30]
Caregiver gender (% male)	50%†	50%†	55%[30]
Caregiver survival	UK[11]	UK[11]	UK[11]
Caregiver weighting	1:1[35]	1:1[35]	1:1[35]
Caregiver bereavement	−0.22; −0.14; −0.09[36,37]	−0.22; −0.14; −0.09[36,37]	−0.03[38]
Caregiver bereavement duration	<5; 5–10; >10 years[36,37]	<5; 5–10; >10 years[36,37]	1 year[38]
Proportion of patients receiving informal care	100%†	100%†	26–86%[39]

*Expert opinion. †Assumption.

Table 3. Utility input parameters

SMA	Patient (SE)	Caregiver (SE)
Not sitting	−0.12 (−0.03)	0.74 (0.18)
Permanent ventilation	−0.24 (−0.06)	
Sitting	−0.11 (−0.03)	
Standing*	0.38 (0.09)	
Walking*	0.62 (0.15)	
Disease-related impact (disutilities)		None
Respiratory function	−0.21 (−0.053)	
Bulbar function	−0.05 (−0.01)	
Scoliosis	−0.10 (−0.03)	

DMD	Patient (SE)	Caregiver (SE)
Early ambulatory	0.699 (0.036)	0.858 (0.017)
Late ambulatory	0.607 (0.029)	0.839 (0.017)
Transfer	0.607 (0.029)	0.784 (0.021)
HTMF, no ventilation	0.224 (0.014)	0.784 (0.021)
No HTMF, no ventilation	0.224 (0.014)	0.784 (0.021)
HTMF, nighttime ventilation	0.146 (0.014)	0.784 (0.021)
No HTMF, nighttime ventilation	0.146 (0.010)	0.810 (0.018)
Full-time ventilation	0.051 (0.010)	0.810 (0.018)

MS	Patient (SE)	Caregiver (SE)
RMS EDSS 0	0.870 (0.045)	−0.002 (0.053)
RMS EDSS 1	0.799 (0.048)	−0.002 (0.053)
RMS EDSS 2	0.705 (0.048)	−0.045 (0.057)
RMS EDSS 3	0.574 (0.052)	−0.045 (0.057)
RMS EDSS 4	0.610 (0.048)	−0.142 (0.062)
RMS EDSS 5	0.518 (0.045)	−0.160 (0.055)
RMS EDSS 6	0.460 (0.051)	−0.173 (0.054)
RMS EDSS 7	0.297 (0.049)	−0.030 (0.038)
RMS EDSS 8	−0.049 (0.047)	−0.095 (0.075)
RMS EDSS 9	−0.195 (0.074)	−0.095 (0.075)
SPMS EDSS 0–9	RMS −0.045 (0.023)	Same as RMS
Relapse (decrement)	−0.071 (0.036)	None

*Patients were assigned the same utility values irrespective of whether they require support in these health states.

Abbreviations

AE, adverse event; CDA-AMC, Canada's Drug Agency – Agence des médicaments du Canada; CHEERS, Consolidated Health Economic Evaluation Reporting Standards; DMD, Duchenne muscular dystrophy; EDSS, Expanded Disability Status Scale; EQ-5D-3L; Euro Quality of Life - 5 Dimensions - 3 Levels; HAS, Haute Autorité de Santé; HEMA, Health Economics Methods Advisory; HRQoL, health-related quality of life; HSE, Health Survey for England; HSUV, Health State Utility Value; HTA, Health Technology Assessment; HTMF, hand-to-mouth function; HUI-3, Health Utilities Index Mark 3; INESSS, Institut national d'excellence en santé et en services sociaux; KCE, Belgian Health Care Knowledge Centre; MS, multiple sclerosis; NCPE, National Centre for Pharmacoeconomics; NICE, National Institute for Health and Care Excellence; PAG, patient advocacy group; PBAC, Pharmaceutical Benefits Advisory Committee; PBS, The Pharmaceutical Benefits Scheme; PV, permanent ventilation; QALY, quality-adjusted life year; RMS, relapsing MS; SAE, serious adverse event; SE, standard error; SMA, spinal muscular atrophy; SMC, Scottish Medicines Consortium; SMN, survival of motor neuron; SPMS, secondary progressive MS; TLV, Tandvårds- och läkemedelsförmånsverket; ZiN, Zorginstituut Nederland.

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