Modelling analysis plan

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A conceptual decision-analytic model with natural history of disease data for multiple system atrophy comparing the interventions best supportive care versus a hypothetical intervention with best supportive care

1. Approach

The aim is to conduct the first cost-effectiveness analysis for multiple system atrophy (MSA). MSA is a rapidly progressing and rare neurodegenerative disorder with a survival of between 6.2 to 9.8 years from the onset of symptoms (Ben-Shlomo, Wenning, Tison and Quinn, 1997; Wenning *et al.*, 1994; Wenning *et al.*, 2013; Low *et al.*, 2015). We have previously recommended early and timely cost-effectiveness modelling for orphan drugs in rare diseases (Grand *et al.*, 2024b). The modelling analysis plan represents a first modelling iteration to provide important information on data gaps and on effectiveness requirements for orphan drugs in MSA. A de novo decision-analytic model will be developed that reflects disease trajectories for patients. However, the analysis will be purely hypothetical and use currently available data, which still ought to provide crucial learnings for further research generation and modelling iterations. Thus, cost-effectiveness results are likely very unreliable at this early stage and people should be very cautious when interpreting results.

2. Methods

The analysis will take a United Kingdom National Health Service (NHS) perspective. The base-case analysis will use a cost-effectiveness threshold of £30,000 per QALY, because £20,000 – 30,000 is regarded as good value for money by NICE (Bouvy, 2024). The highly specialised technology appraisal (HST) is excluded, because the prevalence is between 2 to 5 cases per 100,000 people for MSA as compared to the HST routing criteria of lower than 1 per 50,000 people (York Health Economics Consortium, 2016a; National Institue for Health and Care Excellence, 2024; Fowler, 2011; NHS Trust, 2023).

The data to inform the model will be sourced from published literature and natural history of disease data collected by the European MSA Collaboration Group (Wenning *et al.*, 2013). The model will be developed in the software R together with a Shiny App for user-friendliness and exploration by healthcare and non-healthcare professionals. This software provides the ability for easy sharing of open-source code and enables continuous updating with new data. An approach which has previously been described as living health technology assessment (HTA) (Thokala *et al.*, 2023; Smith, Schneider and Mohammed, 2022).

2.1 Use of rare-disease analogues

The strategy of using rare-disease analogues to fill data gaps in cost-effectiveness analyses for rare diseases was previously explored, but not extensively highlighted (Grand *et al.*, 2024b; Pearson, Rothwell, Olaye and Knight, 2018). The strategy was highlighted for the sourcing of utility values associated with wheelchair confinement for Duchenne's disease (less prevalent) from multiple sclerosis (more prevalent) (Pearson, Rothwell, Olaye and Knight, 2018). Rare-disease analogues for this study were diseases that display similar characteristics but with higher prevalence.

2.2 Model structure

The model structure was informed by clinical experts and literature reviews of MSA and rare-disease analogues e.g., multiple sclerosis, advanced parkinson's disease, and amyotrophic lateral sclerosis (Grand *et al.*, 2024a). The literature searches showed wide use of Markovian (cohort) models where health states were informed by functional rating scales. For example, expanded disability status scale (multiple sclerosis), Hoehn and Yahr states (Parkinson's disease), and Fine'til 9 (amyotrophic lateral sclerosis) (Auguste *et al.*, 2020; Ayati *et al.*, 2021; Ayati, Taheri, Sahraian and Nikfar, 2021; Baharnoori *et al.*, 2022; Chaudhuri *et al.*, 2022; Cortesi *et al.*, 2022; Daroudi *et al.*, 2023; Furneri, Santoni, Ricella and Prosperini, 2019; Ginestal *et al.*, 2023; Giovannoni *et al.*, 2019; Hua *et al.*, 2019; Kalabina *et al.*, 2019; Kremer *et al.*, 2020; Lasalvia *et al.*, 2020; Martins *et al.*, 2023; Michels *et al.*, 2019;

Montgomery *et al.*, 2022; Nakhaipour *et al.*, 2020; Navarro and Betancur, 2023; Pinheiro, Guerreiro, Costa and Miguel, 2020; Poveda *et al.*, 2020; Rezaee *et al.*, 2019; Schur *et al.*, 2021; Spelman *et al.*, 2024; Spelman *et al.*, 2022; Stanisic *et al.*, 2019; Taheri, Sahraian and Yousefi, 2019; Thakore *et al.*, 2020; Visser *et al.*, 2022; Walter, Berger, Bajer-Kornek and Deisenhammer, 2019; Xu *et al.*, 2019; Pahwa *et al.*, 2023). Similarly, hand searches for rare-disease analogues with lower prevalence (rare diseases) corroborated these findings. For example, Huntington disease where a total functional score was combined with active functional decline by Shoulson and Fahn categories (Guzauskas *et al.*, 2024). In addition, spinocerebellar ataxia type 1 where early model health states were stratified by scale for the assessment rating of Ataxia (van Prooije *et al.*, 2023).

The MSA model reflects disease progression by the Unified MSA Rating Scale (UMSARS) IV, which is a global disability scale focussing on motor function (Wenning *et al.*, 2004). Previously, aid-required walking, wheelchair confinement, and bedridden states have also been reported as important motor-function or clinical milestones (Watanabe *et al.*, 2002).

Noteworthy is the relationship between UMSARS IV and these motor-function milestones, because the bedridden milestone is a part of item 5 in UMSARS IV. Explicitly, “totally dependent and helpless. Bedridden”. By contrast, aid-required walking and wheelchair confinement are not included in the UMSARS IV items. Importantly, however, is that these motor-function milestones have been illustrated alongside each of the UMSARS IV items: completely or not completely independent (able to walk), more dependent (aid-required walking), very dependent (wheelchair confinement), and totally dependent (bedridden) (Saulnier *et al.*, 2024). We therefore argue that for decision-analytic modelling that UMSARS IV and motor function milestones (events) are clinical approximations of each other, which have important methodological implications for the ability to conduct cost-effectiveness modelling.

For example, if the data are collected at sufficiently short intervals, patients are expected to transition sequentially through the UMSARS IV items or motor-function milestones. By way of explanation e.g., from very dependent (wheelchair confined) to totally dependent (bedridden) and NOT from more dependent (aid-required walking) to totally dependent (bedridden). If this assumption is valid, in theory, there should be two decision-analytic modelling approaches that could be explored. A Markov modelling approach whereby patients move through health states by their transition probabilities and a partitioned survival (time to event) modelling approach where patients move between health states based on parametric survival equations (York Health Economics Consortium, 2016b). Importantly, for both approaches, is that they do not allow reversal of disease progression e.g., from totally dependent (bedridden) to more dependent (aid-required walking). This is assumption is unarguably aligned with clinical practice as a cure for this progressive disease does not exist.

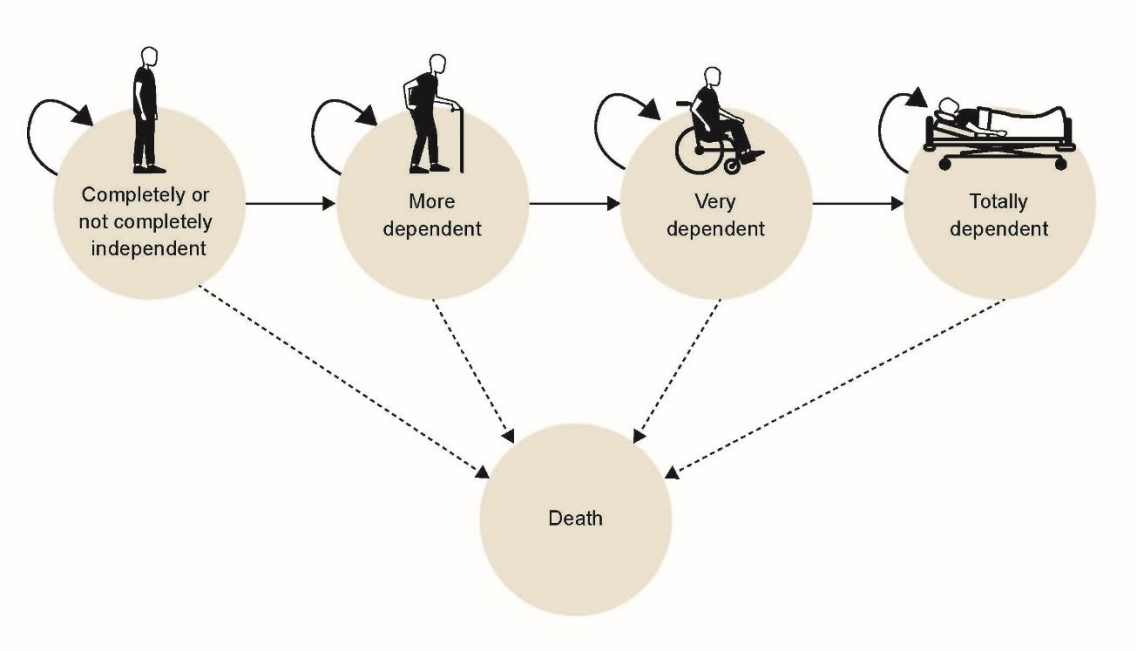
Only the Markov modelling approach will be explored in this analysis. For the Markov model structure, items 1 and 2 from the scale were collapsed into completely or not completely independent as they represent nearly equal costs and health benefits, which was supported by available registry data and a cost-of-illness study (Winter *et al.*, 2011b). However, this is a temporary assumption based on currently available evidence. Death was included as an absorbing health state in the model (Wenning *et al.*, 2013).

UMSARS IV item 1 + 2, 3, 4 and 5 will have walking, aid-required walking, wheelchair confinement, and bedridden illustrations for each health state to align with a previously published study on natural history of disease (Saulnier *et al.*, 2024). This approach ought to be easier to comprehend if

disseminated to non-healthcare professionals e.g., patient organisations rather than solely listing UMSARS IV items. (Watanabe *et al.*, 2002; Wenning *et al.*, 2004).

Figure 1 shows the model structure with health states: completely or not completely independent (walking), more dependent (aid-required walking), very dependent (wheelchair confinement), totally dependent (bedridden) and death (all-cause and disease mortality).

Figure 1: Model structure for multiple system atrophy reflecting modified UMSARS IV



2.3 Target Populations

The targeted population for this analysis is people living with MSA, regardless of whether clinically possible or probable diagnostic criteria are applied (Gilman *et al.*, 2008). The inclusion and exclusion criteria are aligned with the European MSA collaboration work package III. The work package is data on file (not published); however, the criteria are reflected in published literature. For example, The natural history of multiple system atrophy: a prospective European cohort study (Wenning *et al.*, 2013).

Inclusion criteria

The target population encompasses the secondary data collected by European MSA Study Group, wherein the inclusion criteria were clinically possible or probable MSA and provision of written informed consent (Wenning *et al.*, 2013).

Exclusion criteria

The exclusion criteria are onset under 30 years of age, family history of a similar disorder, secondary cause by history, secondary cause by investigation, hallucinations unrelated to drugs, dementia according to DSM IV (Diagnostic and Statistical Manual of Mental Disorders – fourth edition), prominent slowing of vertical saccades, vertical supranuclear palsy (down/upward gaze palsy), aphasia, alien limb syndrome, parietal dysfunction, and generalised areflexia.

2.4 Interventions

The interventions are best supportive care versus a hypothetical intervention and best supportive care because disease-modifying treatments are not yet available.

2.5 Key Model Choices and Assumptions

Table 1 lists the assumptions that were applied for the modelling.

Table 1: Assumptions applied to the modelling analysis

	Assumptions	Consequence
1	It is assumed that item 1 and 2 from UMSARS IV reflect close to equal costs and quality of life. In support Winter et al. 2011, who initially made this grouping for costs. Secondly, data on file, utility for items 1 and 2 were: 0.604 (n = 12) and 0.574 (n = 75).	Item 1 and 2 from UMSARS IV is collapsed into one health state in the model structure.
2	For data on file, we assume that it is missing completely at random.	Only complete cases will be analysed, and the number of observations will be reduced. Also, subjects with one observation were excluded.
3	We assume that Germany cost data can be used to approximate costs in United Kingdom.	We will inflate (2011 to 2024) and adjust for currency (€ to £) and use cost data stratified across health states from Winter et al 2011 (Winter *et al.*, 2011b). McCrone did not stratify by health states, although they took a United Kingdom perspective (McCrone *et al.*, 2011).
4	We assume that patients cannot transition backwards in model, because clinically, the disease cannot revert once progressed. Only few backward transitions were observed in data, but this is likely due day-to-day clinical variations.	Patients were not allowed to reverse their progression in the Markov model.

2.6 Input parameters

For the input parameter, file, variable and prefix names will follow the DARTH coding framework for R (Alarid-Escudero *et al.*, 2019; Alarid-Escudero *et al.*, 2023). Table 2 contains an overview of R inputs e.g., for probabilistic sensitivity analysis (PSA) and for parameters that can be modified by Shiny App users.

Table 2: R modelling inputs

Parameter type	Parameter name	Value	PSA	Shiny user specification
Model specifications				
Number of cycles	n_cycles	528	constant	N/A
Names of health states	v_names_states	Ci, Md, Vd, Td, D	constant	N/A
Background all-cause mortality	v_p_Dage	age-dependent	constant	N/A
Discount rate costs	d_c	3.5	constant	0 - 1
Discount rate QALYs	d_e	3.5	constant	0 - 1

Number of PSA samples	n_sim	1000	constant	100-10000
Transition probabilities (across all trial visits)				
Ci to Md	p_CiMd	0.086	rbeta (shape1 = 0.0515, shape2 = 0.5458)	N/A
Ci to Vd	p_CiVd	0.0047	constant	N/A
Ci to Td	p_CiTd	0.000051	constant	N/A
Ci to D	p_CiD	0.000033	constant	
Md to Vd	p_MdVd	0.010	rbeta (shape1 = 0.1114, shape2 = 1.045)	N/A
Md to Td	p_MdTd	0.0016	constant	
Md to D	p_MdD	0.0010	constant	N/A
Vd to Td	p_VdTd	0.030	rbeta (shape1 = 0.1102, shape2 = 3.5233)	N/A
Vd to D	p_VdD	0.020	rbeta (shape1 = 0.07, shape2 = 3.4874)	N/A
Td to D	p_TdD	0.031	rbeta (shape1 = 0.0343, shape2 = 1.059)	N/A
D to D	p_DD	1	constant	N/A
Treatment modifier for transitions probabilities (slowing of disease progression)				
Relative risk treatment modifier for transition probabilities	rr_trt_mod_p	0.5	constant	0.01 - 1
Probabilities of events (monthly)				
Probability of urinary disorders	p_UD	0.058	rbeta (73; 70)	N/A
Probability of hypotension disorders	p_HD	0.067	rbeta (81; 62)	N/A
Probability of bowel disorders	p_BD	0.582	rbeta (83; 60)	N/A
Treatment modifier for probability of events (reduction in number of events)				
Relative risk treatment modifier for clinical events	rr_trt_mod_e	0.5	constant	0.01 - 1
Total costs (monthly)				
Costs for Ci	c_Ci	987.75	gamma (shape = 4, scale = c_Ci/4)	£ 0 – 100,000
Costs for Md	c_Md	2000.10	gamma (shape = 4, scale = c_Md/4)	£ 0 – 100,000

Costs for Vd	c_Vd	3679.37	gamma (shape = 4, scale = c_Vd/4)	£ 0 – 100,000
Costs for Td	c_Td	3679.37	gamma (shape = 4, scale = c_Td/4)	£ 0 – 100,000
Price of hypothetical intervention (monthly)	c_Trt	100.00	constant	£ 0 – 10,000
Utility values				
Utility for Ci	u_Ci	0.5787011	rbeta (125.68; 91.50)	N/A
Utility for Md	u_Md	0.4272593	rbeta (86.68; 116.20)	N/A
Utility for Vd	u_Vd	0.1435197	rbeta (27.44; 163.75)	N/A
Utility for Td	u_Td	-0.1255000	constant	N/A
Disutility values				
Disutility value for urinary disorders*	du_UD	0.0054	rbeta (0.55; 102.05)	N/A
Disutility value for hypotension disorders**	du_HD	0.013	constant	N/A
Disutility for bowel disorders***	du_BD	0.194	constant	N/A
List of terms used in literature: * Urinary disorder, bladder symptoms, urinary retention, incomplete bladder emptying, urinary incontinence ** Orthostatic and supine hypotension *** Constipation and faecal incontinence. Note that a selection of values is rounded for better illustration.				

Transition probabilities for comparators

European MSA (EMSA) data are captured at baseline, 6, 12, 18 and 24 months, which can be used to calculate transition probabilities across UMSARS IV. Our initial approach was to use a non-parametric count method, but it showed that transition probabilities were not constant over the 6 monthly intervals, which could be due to few subjects or insufficient follow-up. See Table 3 for variation of transitions using a non-parametric count method.

Table 3: Lowest and highest transition probabilities at six-monthly intervals

	Completely or not completely independent (Ci)	**More dependent (Md)**	**Very dependent (Vd)**	**Totally dependent (Td)**	**Death (D)**
Completely or not completely independent (Ci)	0.55 - 0.8	0.2 - 0.29	0 - 0.16	0 – 0.02	N/A
More dependent (Md)	N/A	0.42 - 0.89	0.11 - 0.54	N/A	0 – 0.06
Very dependent (Vd)	N/A	N/A	0.63 - 0.7	0.2 - 0.26	0.05 - 0.17
Totally dependent (Td)	N/A	N/A	N/A	0.55 – 0.88	0.12 - 0.45

Death (D)	N/A	N/A	N/A	N/A	1

A multistate modelling approach was used as a substitute in response to the issue of variability of transition probabilities over discrete time. The method fits a multistate model to the natural history of disease data using state occupation and time. The calculations were made with the msm R package, which uses maximum likelihood estimation to endogenously estimate transition probabilities. Although, the msm package was designed for continuous time models, it can be used for discrete time assuming that there is a continuous process underlying the data (Srivastava, Latimer and Tappenden, 2021; Jackson, 2011).

The transition intensity matrix Q shows instantaneous transitions or a snapshot of the Markov process. The multistate model is fitted to the data, but controlled by the matrix Q (Jackson, 2011). The matrix Q is specified to best reflect clinical reality if patient transitions were captured at accurate time points. For example, patients are likely to deteriorate sequentially through the health states. In other words, not moving from Completely or not completely independent (Ci) to totally dependent (Td), which in the observed data may be due to six-monthly time intervals for data collection being too long.

$$Q = \begin{pmatrix} -(q12 + q15) & q12 & 0 & 0 & q15 \\ 0 & -(q23 + q25) & q23 & 0 & q25 \\ 0 & 0 & -(q34 + q35) & q34 & q35 \\ 0 & 0 & 0 & -q45 & q45 \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix}$$

Zeros in the Q matrix illustrates that transitions are not possible through these states if time was accurately captured at each transition. An initial value for transition intensity is specified in R software where transitions are possible. However, for the zeros, if time intervals are long, then patients can still transition through these states. What is observed as Ci to Vd in the transition matrix, is in theory, Ci to Md to Vd within the time interval t. In Table 4 this is, for example, the case for a cycle length of 6 months, which is why we use a cycle length of 1 months, which brings the e.g., p_CiVd closer to zero.

Table 4: Naming conventions for transitions

	Completely or not completely independent (Ci)	**More dependent (Md)**	**Very dependent (Vd)**	**Totally dependent (Td)**	**Death (D)**
Completely or not completely independent (Ci)	p_CiCi	p_CiMd	p_CiVd	p_CiTd	p_CiD
More dependent (Md)	N/A	p_MdMd	p_MdVd	p_MdTd	p_MdD
Very dependent (Vd)	N/A	N/A	p_VdVd	p_VdTd	p_VdD
Totally dependent (Td)	N/A	N/A	N/A	p_TdTd	p_TdD

Death (D)	N/A	N/A	N/A	N/A	1

Table 5 shows the transition calculations for best supportive care, which account for both disease-specific and age-dependent all-cause mortality (*v_p_Dage*). All-cause mortality will reflect death rates by age group in England and Wales (Our world in data, 2015).

Table 5: Transition calculations for best supportive care

	Completely or not completely independent (Ci)	**More dependent (Md)**	**Very dependent (Vd)**	**Totally dependent (Td)**	**Death**
Completely or not completely independent (Ci)	(1 - v_p_Dage[i]) * (1 - (p_CiMd + p_CiVd + p_CiTd + p_CiD))	(1 - v_p_Dage[i]) * p_CiMd	(1 - v_p_Dage[i]) * p_CiVd	(1 - v_p_Dage[i]) * p_CiTd	(1 - v_p_Dage[i]) * p_CiD + v_p_Dage[i]
More dependent (Md)	N/A	(1 - v_p_Dage[i]) * (1 - (p_MdVd + p_MdTd + p_MdD))	(1 - v_p_Dage[i]) * p_MdVd	(1 - v_p_Dage[i]) * p_MdTd	(1 - v_p_Dage[i]) * p_MdD + v_p_Dage[i]
Very dependent (Vd)	N/A	N/A	(1 - v_p_Dage[i]) * (1 - (p_VdTd + p_VdD))	(1 - v_p_Dage[i]) * p_VdTd	(1 - v_p_Dage[i]) * p_VdD + v_p_Dage[i]
Totally dependent (Td)	N/A	N/A	N/A	(1 - v_p_Dage[i]) * (1 - p_TdD)	(1 - v_p_Dage[i]) * p_TdD + v_p_Dage[i] _p
Death (D)	N/A	N/A	N/A	N/A	p_DD = 1

A user-specified treatment modifier, *rr_trt_mod_p*, will reflect a reduction in relative risk for the hypothetical intervention. It is incorporated in the transition probability matrix by multiplication to reflect a disease modifying intervention that slows progression of disease. However, not for the state totally dependent as the quality of life in this state is worse than death with a negative utility value, which is why treatment may be unethical at this severity level. Similarly, no hypothetical intervention costs are assigned. See Table 6 for transition probabilities with a hypothetical intervention and best supportive.

Table 6: Transition probabilities for best supportive care and hypothetical intervention

	Completely or not completely independent (Ci)	**More dependent (Md)**	**Very dependent (Vd)**	**Totally dependent (Td)**	**Death**

Completely or not completely independent (Ci)	(1 - v_p_Dage[i]) * (1 - (p_CiMd + p_CiVd + p_CiTd + p_CiD) * rr_trt_mod_p)	(1 - v_p_Dage[i]) * p_CiMd * rr_trt_mod_p	(1 - v_p_Dage[i]) * p_CiVd * rr_trt_mod_p	(1 - v_p_Dage[i]) * p_CiD * rr_trt_mod_p + v_p_Dage[i]	(1 - v_p_Dage[i]) * p_CiD * rr_trt_mod_p + v_p_Dage[i]
More dependent (Md)	N/A	(1 - v_p_Dage[i]) * (1 - (p_MdVd + p_MdTd + p_MdD) * rr_trt_mod_p)	(1 - v_p_Dage[i]) * p_MdVd * rr_trt_mod_p	(1 - v_p_Dage[i]) * p_MdTd * rr_trt_mod_p	(1 - v_p_Dage[i]) * p_MdD * rr_trt_mod_p + v_p_Dage[i]
Very dependent (Vd)	N/A	N/A	(1 - v_p_Dage[i]) * (1 - (p_VdTd + p_VdD) * rr_trt_mod_p)	(1 - v_p_Dage[i]) * p_VdTd * rr_trt_mod_p	(1 - v_p_Dage[i]) * p_VdD * rr_trt_mod_p + v_p_Dage[i]
Totally dependent (Td)	N/A	N/A	N/A	(1 - v_p_Dage[i]) * (1 - p_TdD))	(1 - v_p_Dage[i]) * p_TdD + v_p_Dage[i]
Death (D)	N/A	N/A	N/A	N/A	p_DD = 1

The approach of a treatment modifier was inspired by a cost-effectiveness analysis in human immunodeficiency virus (HIV) by Chancellor and colleagues, which is further highlighted in the book Decision Modelling for Health Economic Evaluation, wherein transition probabilities are adjusted by a relative risk reduction from a meta-analysis for combination therapy as compared to monotherapy (Chancellor *et al.*, 1997; Briggs, Sculpher and Claxton, 2006).

Cost data

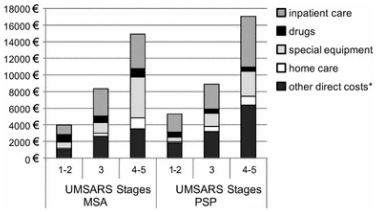
Background information on cost data:

Cost data is limited. At their time of publication, Winter et al. (2011b) and McCrone et al. (2011) both reported that no previous studies existed. Winter and colleagues investigated German patients and are the only ones to stratify costs by UMSARS IV, a global disability scale (Wenning et al., 2004). Moreover, they showed that significant cost drivers were: age groups in years, marital status, age at disease onset, depression, and UMSARS IV (Winter et al., 2011b). McCrone and colleagues covered France, Germany, and the United Kingdom. Patients required a range of services, but informal care was the main contributor of costs. Moreover, costs and severity of disease were correlated. In fact, McCrone and colleagues hold the view that their data support the hypothesis that disease modifying interventions can decelerate or halt progression of disease, and hence, reduce the economic burden. (McCrone et al., 2011).

The simplest way to populate the model is to use data reported by the Winter paper across UMSARS IV, which will require adjustment for inflation from 2011 to 2024, and conversion to British pounds sterling (Winter *et al.*, 2011b). McCrone does not include stratification across UMSARS IV (McCrone *et al.*, 2011). Figure 2 is included with permission from authors and shows the stratification of costs, from which, the cost data in Table 7 are estimated.

Figure 2: Cost data stratified by UMSARS IV from Winter et al 2011

From: Cost-of-illness in multiple system atrophy and progressive supranuclear palsy



Semi-annual direct costs stratified by disease severity. *other direct costs consist of outpatient care, ancillary treatment, transport, copayments

Table 7: Cost data estimated from Figure 1 in Winter et al 2011 (six-monthly)

Costs from paper (six-monthly)	Inpatient care	Drugs (BSC)	Special equipment	Home care	Other direct costs
Completely or not completely independent	€ 1,200.00	€ 800.00	€ 800.00	€ -	€ 1,200.00
More dependent	€ 3,000.00	€ 1,200.00	€ 1,200.00	€ 200.00	€ 2,500.00
Very dependent	€ 4,000.00	€ 1,300.00	€ 4,200.00	€ 1,600.00	€ 3,800.00
Totally dependent	€ 4,000.00	€ 1,300.00	€ 4,200.00	€ 1,600.00	€ 3,800.00

The cost data from Table 7 are converted from euros to pound using 2011 tariffs and adjusted for inflation. Conversion and inflation rates are available from Table 8 and converted to monthly cost data for use in the analysis from Table 9.

Table 8: Rates for conversion and inflation adjustments

Conversion rate (1 € to £)	£ 0.8872	Source: Exchange Rates United Kingdom: https://www.exchangerates.org.uk/EUR-GBP-spot-exchange-rates-history-2010.html
Inflation adjustment	£ 1.67	Source: Office for National Statistics, United Kingdom: https://www.ons.gov.uk/economy/inflationandpriceindices/timeseries/czbh/mm23

The converted data for analysis is available from Table 9.

Table 9: Converted costs data for use in analysis (monthly)

Converted costs for analysis (monthly)	Inpatient care	Drugs (BSC)	Special equipment	Home care	Other direct costs	Total

Completely or not completely independent	£ 296.32	£ 197.55	£ 197.55	£ -	£ 296.32	£ 987.75
More dependent	£ 740.81	£ 296.32	£ 296.32	£ 49.387	£ 617.34	£ 2000.10
Very dependent	£ 987.75	£ 321.02	£ 1037.14	£ 395.10	£ 938.36	£ 3679.37
Totally dependent	£ 987.75	£ 321.02	£ 1037.14	£ 395.10	£ 938.36	£ 3679.37

Quality-of-life data: health states

Background information on EQ-5D data

Quality of life studies without follow-up were classified as either cross-sectional or mixed-methods studies. Interestingly, for cost-effectiveness modelling purposes, three studies reported mean EQ-5D index values for MSA with standard deviations, and they were between 0.2 (0.3) to 0.558 (0.276) (Schrag et al., 2006; Schrag et al., 2010; Xiao et al., 2022). Others reported on the distribution of MSA patients across EQ-5D dimensions (Winter et al., 2011a; Schrag et al., 2007; Xiao et al., 2022; Schrag et al., 2010).

We used the R package "eq5d" with United Kingdom EQ-5D-3L value sets to calculate utility index scores from the EMSA data (data on file) (Morton and Singh, 2024). In the probabilistic sensitivity analysis UMSARS IV: 5, which is negative, is kept constant for simplicity and to avoid sampling implausible values e.g., lower limit -0.594 of EQ-5D-3L in United Kingdom.

Table 10: EQ-5D-3L (utilities) for UMSARS IV health states

UMSARS IV	Mean Index Score	N	Standard error	Alpha	Beta
1+2	0.5787011	87	0.03342859	125.68045	91.49633
3	0.4272593	81	0.03464457	86.68328	116.19888
4	0.1435197	152	0.02529041	27.43868	163.74532
5	-0.1255000	60	N/A	N/A	N/A

Quality-of-life data: clinical events

Background information natural history of disease data

Survival was followed in five studies by either Kaplan-Meier or Cox-regression curves. The median survival from symptom onset to death ranged from 6.4 – 9.8 years (Cao et al., 2018; Foubert-Samier et al., 2020; Low et al., 2015; Watanabe et al., 2002; Wenning et al., 2013). In addition, studies measured stridor, falls, orthostatic hypotension, depression, apathy, delusions, and urinary incontinence (Cao et al., 2018; Foubert-Samier et al., 2020; Jecmenica-Lukic et al., 2021; Jecmenica-Lukic et al., 2018; Kollensperger et al., 2007; Saulnier et al., 2024). Lastly, two studies monitored clinical manifestations or milestones of progression: falls per day, unintelligible speech,

and time to aid-required walking, wheelchair confinement, and bedridden state (Watanabe et al., 2002; Wenning et al., 2013).

Short-term (acute) clinical events were included in the analysis if they are independent of model health states (motor function) and expected to result in a temporary reduction in quality of life, which may not be captured by the six-monthly EQ-5D-3L responses. However, this is an area that warrants further research for economic modelling. Nonetheless, the clinical events were grouped by hypotension, urinary or bladder, and bowel disorders in Table 11. Only disutilities will be included for clinical events to avoid double-counting as their cost may be captured in the aggregated cost data.

Probabilities for clinical events

As shown in Table 11 the probability of orthostatic hypotension was frequently reported in comparison to supine hypotension which was reported once. Similarly, urinary disorders were often reported. Despite of varying nomenclature, they broadly seemed to concern mainly urinary incontinence and incomplete bladder emptying. Less studies were concerned with bowel disorders (constipation and faecal incontinence). For this analysis, probability of event data was sourced from a European cohort for all three categories: hypotension disorders, urinary disorders, and bowel disorders (Wenning *et al.*, 2013).

A user-specified treatment modifier, *rr_trt_mod_e* was multiplied with event probabilities for the hypothetical intervention, but similarly to the *rr_trt_mod_p, it* is not applied to the totally dependent health state. We assume probabilities remain constant over time.

Table 11: Overview of probabilities for clinical events in multiple system atrophy. The data from Wenning et al 2013 is percentage at baseline, which are used in the analysis.

Clinical events	Probabilities	References
Hypotension disorders	71 % orthostatic hypotension / 47.9 % supine hypotension (n = 261)	(Foubert-Samier *et al.*, 2020)
	60 % orthostatic hypotension (n = 27)	(Kollensperger *et al.*, 2007)
	67.4 % orthostatic hypotension (n = 536)	(Saulnier *et al.*, 2024)
	56.7 % orthostatic hypotension (n = 141)	**(Wenning *et al.*, 2013)**
Urinary or bladder disorders	88.8 % bladder symptoms (n = 80);	(Cao *et al.*, 2018)
	48 % urinary retention / 52 % urinary incontinence (n = 27)	(Kollensperger *et al.*, 2007)
	83 % incomplete bladder emptying / 87 % urinary incontinence (n = 175)	(Low *et al.*, 2015)
	68.1 % urinary disorder (n = 536)	(Saulnier *et al.*, 2024)
	73 % urinary incontinence **/ 51.1 % incomplete bladder emptying (n = 141)**	**(Wenning *et al.*, 2013)**
Bowel disorders	**58.2 % constipation (n = 141)**	**(Wenning *et al.*, 2013)**
	87 % constipation / 29 % faecal incontinence (n = 175)	(Low *et al.*, 2015)

Disutility values for clinical events

We identified the EQ-5D-5L value for MSA with and without orthostatic hypotension, which was 0.571 and 0.638, respectively. The disutility decrement for this analysis can then be estimated by subtraction to - 0.067 (Xiao *et al.*, 2022). The disutility is higher than in an economic evaluation of multiple sclerosis, where hypertension was - 0.037 but originally sourced from a time-trade off analysis by Stein and colleagues (Stein *et al.*, 2002; Lazzaro *et al.*, 2022). A disutility was not identified for supine hypotension, which is why the disutility value for orthostatic hypotension was used as a proxy for hypotension disorders (Foubert-Samier *et al.*, 2020; Kollensperger *et al.*, 2007; Saulnier *et al.*, 2024; Wenning *et al.*, 2013). This means that we may underestimate the disutility for hypotension disorders due to missing data.

For bowel disorders, cost-effectiveness analyses for multiple sclerosis included a disutility of - 0.240 for gastrointestinal disorders, but the value was not possible verify. The papers cited a non-referenced network meta-analysis or could not be found in the original reference provided (Pinheiro, Guerreiro, Costa and Miguel, 2020; Michels *et al.*, 2019). Instead, we explored the utility for other functional intestinal disorders (ICD-10 Code K59.1 functional diarrhea and K59.09 other constipation) which includes constipation (ICD10Data, 2024). The utility value was 0.635, which subtracted from the United Kingdom population average (0.829) yields a utility decrement of - 0.194 (Falk Hvidberg and Hernández Alava, 2023). This estimate will be used in the analysis because it seemed most conservative.

The costs of urinary tract infections were commonly included in economic evaluations for rare-disease analogues, but disutilities were not reported (Acosta *et al.*, 2021; Ayati, Taheri, Sahraian and Nikfar, 2021; Hunter *et al.*, 2021; Martins *et al.*, 2023). For MSA, urinary disorders e.g., incontinence and incomplete bladder emptying may they lead to uncontrollable urinary tract infections (Papatsoris, Papapetropoulos, Singer and Deliveliotis, 2008). A MSA study (n = 21) reported that urinary tract infection was the secondary cause of death (23.8%) after cardiopulmonary arrest (33.3%). Similarly, recurrent lower urinary tract infections occurred in 61.3% patients (Papapetropoulos *et al.*, 2007). In the larger study by Wenning and colleagues, urinary disorders ranged between 73% (urinary incontinence) and 51.1% (incomplete bladder emptying). It was decided to use 51.1% for the probability of having urinary disorders that could lead to urinary tract infections to maintain a conservative modelling approach (Wenning *et al.*, 2013).

The utility values for recurrent urinary tract infections in English-speaking women varied but were in the range 0.63 to 0.85 (Le Neveu *et al.*, 2023; Thompson *et al.*, 2023). Similarly, a systematic review of EQ-5D scores showed large variation for diseases of the genitourinary system e.g., disutilities were between -0.49 (urinary incontinence) to + 0.01 (early kidney disease) (Van Wilder *et al.*, 2019). For this analysis, the disutility value (-0.0054) for urinary tract disorder (ICD-9 599) was sourced from a United Kingdom EQ-5D catalogue (Sullivan, Slejko, Sculpher and Ghushchyan, 2011), but may not fully reflect the severity of recurrent lower urinary tract infections in MSA.

Table 12: Overview of disutilities for clinical events in the analysis

Clinical events	Disutility	Reference:
Hypotension disorders	-0.067	Calculated from (Xiao et al., 2022)
Urinary or bladder disorders	-0.0054	(Sullivan, Slejko, Sculpher and Ghushchyan, 2011)
Bowel disorders	- 0.194	Calculated from (Falk Hvidberg and Hernández Alava, 2023)

2.7 Model Outcomes

The cost-effectiveness will be estimated for the comparators best support care versus a hypothetical intervention and best support care because there are no available disease modifying treatments. The outcome of the analysis will be cost per quality adjusted life years (QALYs) over a time horizon of 44 years (528 model cycles). The analysis will follow National Institute for Health and Care Excellence (NICE) guidelines for economic evaluation e.g., discounting costs and health effects by 3.5 % (National Institue for Health and Care Excellence, 2022).

2.8 Analysis

The cost-effectiveness will be reported as the incremental cost-effectiveness ratio (ICER) comparing the difference in costs and effects across the interventions: best supportive care versus a hypothetical intervention and best supportive care.

Scenario analyses will be performed to identify the key drivers of results. A PSA will be performed wherein parameters are simultaneously and randomly sampled across the PSA distributions reported in Table 2.

Early model validation will take place. First, the modelling analysis plan will be reviewed by health economists and medical specialists. Secondly, model validation will take place through the means of face validation e.g., test if parameter variation results in logic changes to the cost and effects. Thirdly, review of R code to assert that no errors were made and making it open source for continued scrutiny. Finally, the outputs can later be compared to natural history of disease, clinical trial data or partitioned survival modelling.

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