DOCTOR OF PHILOSOPHY

Health Economics and Motor Neurone Disease: Evidence for health technology assessments

Moore, Alan

Award date:
2021

Awarding institution:
Bangor University

Health Economics and Motor Neurone Disease: Evidence for health technology assessments

By

Alan Moore

A thesis submitted to Bangor University in partial fulfilment of the requirements for the degree of Doctor of Philosophy

September 2020

Centre for Health Economics and Medicines Evaluation (CHEME), Bangor University

Declaration and Consent

Yr wyf drwy hyn yn datgan mai canlyniad fy ymchwil fy hun yw'r thesis hwn, ac eithrio lle nodir yn wahanol. Caiff ffynonellau eraill eu cydnabod gan droednodiadau yn rhoi cyfeiriadau eglur. Nid yw sylwedd y gwaith hwn wedi cael ei dderbyn o'r blaen ar gyfer unrhyw radd, ac nid yw'n cael ei gyflwyno ar yr un pryd mewn ymgeisiaeth am unrhyw radd oni bai ei fod, fel y cytunwyd gan y Brifysgol, am gymwysterau deuol cymeradwy.

I hereby declare that this thesis is the results of my own investigations, except where otherwise stated. All other sources are acknowledged by bibliographic references. This work has not previously been accepted in substance for any degree and is not being concurrently submitted in candidature for any degree unless, as agreed by the University, for approved dual awards.

Table of contents

3- Economic studies in Motor Neurone Disease: a systematic methodological review: Search strategy to identify published economic evaluations, costs and utility studies (Chapter two)
4- Supplementary appendices for chapter 3 - Additional mapping information: additional mapping models, parameter coefficients and standard errors of selected models
5- Supplementary appendices for chapter 4 – Cost sources and overlap of Kings and MiToS staging systems
6- Consolidated Health Economic Evaluation Reporting Standards (CHEERS) Statement checklist for the economic evaluation of edaravone for the treatment of Motor Neurone Disease in the United Kingdom using a Markov modelling approach (Chapter five)

List of tables

List of figures

List of publications and presentations

The following publications have resulted from work in this thesis. References are provided below, with published versions provided in the appendix of this thesis.

Chapter two

- Moore A, Young CA, Hughes DA. **Economic Studies in Motor Neurone Disease: A Systematic Methodological Review**. Pharmacoeconomics. 2017 Apr;35(4):397-413. (Chapter two)

Chapter three

- Moore A, Young CA, Hughes DA. **Mapping ALSFRS-R and ALSUI to EQ-5D in Patients with Motor Neurone Disease**. Value in Health. 2018 Nov;21(11):1322-1329**.**

Chapter four

- Moore A, Young CA, Hughes DA. **Health Utilities and Costs for Motor Neurone Disease**. Value in Health. 2019 Nov;22(11):1257-1265

Contribution of the candidate to the above published works:

- Produced first drafts and revised manuscripts critically for important intellectual content. Provided substantial contributions to the conception, design of the work, the acquisition, analysis, and interpretation of data for the work. Gave final approval of the version to be published. Agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

The following poster presentations resulted from work in this thesis:

- Economic Studies in Motor Neurone Disease: A Systematic Methodological Review. MNDA international symposium 2016 Dublin
- Mapping ALSFRS-R and ALSUI to EQ-5D in Patients with Motor Neurone Disease. MNDA international symposium 2017 Boston

Acknowledgements

I wish to acknowledge and thank my supervisors Professor Dyfrig Hughes and Professor Carolyn Young for all their guidance during my studies. I have learnt so much from them and their expertise. They both have inspired me greatly with their dedication and work ethic in their respective fields.

I want to thank all those involved in the TONiC study, including people with MND who agreed to participate. This resource proved to be so valuable in this thesis. A huge amount of thanks must go to the Motor Neurone Disease Association UK who provided funding for this studentship.

I would also like to thank my partner Sue Wei. Her support throughout has been vital. I cannot thank you enough for your patience and understanding as I completed this thesis. Another big thank you goes to my grandmother Susan. She always encouraged me to do my best and achieve more. To my parents I also owe a huge amount, thank you both for everything.

My friends have been a constant source of support through the highs and lows of this period of study. Special mentions go to Dan, Rio, Emil, Gavin, Dylan, Jen, Rik, John and Hilary, Tom and Abby.

I must acknowledge the support I received from my friends and work colleagues at NICE – who were always interested in my research and all the staff and students at CHEME in Bangor University, for their friendship.

I dedicate this thesis to Ellen and Charlotte.

Glossary

Term	Description
ALSFRS-R	The most commonly used measurement in MND clinical trials
ALSUI	An MND disease-specific preference-based utility measure
Cost-benefit analysis	A comparison of at least 2 interventions in which both costs and benefits (health outcomes etc) are expressed in monetary terms.
Cost-utility analysis	Cost-effectiveness analysis which compares at least 2 interventions in terms of incremental cost per QALY. Cost-utility is the preferred analysis for NICE technology appraisals.
Discounting	The rate (usually annually) at which future benefits and costs are reduced by to estimate a present value for these outcomes. This is done as future gains are valued less than those accrued in the present and future costs are considered preferable to costs incurred earlier.
EQ-5D	A generic preference-based utility measure and the preferred source for health utility data for NICE technology appraisals.
EQ-VAS	The visual analogue component of the EQ-5D measure, which is not preference-based but is reported to validate the utilities produced by the EQ-5D.
Extra-welfarism	Broadens the evaluative space defined by welfarism to include additional considerations along with utility.
Health-related quality of life (HR-QoL)	A measure which estimates the impact of health on a person's quality of life.
Health Technology Assessment (HTA)	The process by which a new health technology is assessed as to whether it is value for money and whether it should be funded from a healthcare budget.
Kings staging	A commonly used clinical staging system to monitor MND disease progression. The Kings staging system focuses on the number of body region affected by MND.
Incremental cost-effectiveness ratio (ICER)	A measure showing the economic value of an intervention in terms of incremental benefits provided divided by incremental costs of the intervention.
Intervention	A new potential healthcare treatment being compared against current treatment options.
Mapping	The term given to the statistical process of linking two different measurements/questionnaires together via the use of an algorithm.
Modelling	A health economic model is a simplified description of the treatment pathway and the specific healthcare decision problem. Models can be used to extrapolate data to provide outcome measurements beyond those in clinical trials.
MiToS staging	A commonly used MND clinical staging model which focuses on the number of functioning domains in which

	independence has been lost.
P value	The probability that a result has occurred by chance – the smaller a p value the more likely it has not occurred by chance.
Probabilistic sensitivity analysis	When all parameter inputs in a model are varied at the same time by applying underlying distributions around input values. Usually repeated many times (e.g 10,000) with results averaged. Deemed more accurate than deterministic analysis (which use only point estimates).
Quality-adjusted life year (QALY)	1 Quality-adjusted life year is equal to 1 year of perfect health. The measure combines length of life and quality of those life years resulting from alternative interventions.
Randomised controlled trial (RCT)	The gold standard clinical trial design in which participants are randomly allocated to treatment groups to reduce the level of bias in results. This should ensure an even split in terms of key prognostic characteristics between treatment groups in the trial.
Scenario analysis	Analysis which estimates the impact of a change in assumptions used within a model.
Sensitivity analysis	Analysis which estimates the impact of changing one or more input parameters to cost-effectiveness results.
Statistical significance	Where a result is not likely to have occurred due to chance and is likely to have occurred due to an intervention. Usually estimated through a small p value (e.g less than 0.05)
Systematic review	A comprehensive review with a clearly expressed research question answered by a systematic and reproducible search strategy.
Utility	A value derived from the desirability of a given health state.
Welfare economics	Focuses on the sum of individual utility as the relevant outcome of evaluations.

Key Abbreviations

	Description
ALS	Amyotrophic Lateral Sclerosis
ALSFRS-R	Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised
ALSUI	Amyotrophic Lateral Sclerosis Utility Index
CBA	Cost-benefit analysis
CEA	Cost-effectiveness analysis
EMA	European Medicines Agency
FDA	Food and Drug Administration
HTA	Health Technology Assessment
HST	Highly Specialised Technologies
ICER	Incremental Cost-effectiveness Ratio
MND	Motor Neurone Disease

NICE	National Institute of Health and Care Excellence
NHS	National Health Service
PRO-ACT	Pooled Resource Open-Access ALS Clinical Trials
PSA	Probabilistic sensitivity analyses
TONiC	Trajectories of Outcome in Neurological Conditions
QALY	Quality adjusted life year

Abstract

Background

Motor Neurone Disease (MND) is a devastating condition, leading to progressive neurodegeneration resulting in reduced functioning. It is a fatal condition, with death occurring around 3 years from symptom onset. Few treatment options exist currently, with only 1 disease-modifying (riluzole) recommended for use in the National Health Service (NHS) to date. With research on-going into potential new treatments for MND, there is a need for a robust health economic framework by which to assess estimate their value, long-term health benefits and costs. This thesis aims to identify key considerations and challenges in health technology assessment (HTA) of new MND treatments and to provide empirical data and analysis which can be used in these HTAs.

Methods

A range of health economic methods are used. These include a systematic review to highlight current evidence gaps and critique the methods used in published studies. Statistical mapping using two commonly used models (ordinary least squares [OLS] and Tobit regression) is undertaken to link MND specific measures to the EQ-5D-5L, both directly and indirectly. Cross-sectional data is utilised from the Trajectories of Outcome in Neurological Conditions (TONIC) study to estimate health utility and costs for two commonly used MND staging systems (Kings and MiToS). A Markov model approach is used to estimate the cost-effective of edaravone, a potential new MND treatment, using data from TONiC study and the Pooled Resource Open-Access ALS Clinical Trials (PRO-ACT) dataset (a large dataset of patient level data from failed MND trials) and results are presented from a UK health payer perspective.

Results

43 studies were included in the systematic review. This review showed that the current evidence base for health economic evaluations in MND is limited, with few studies reporting results by relevant disease measures. It is possible to map from the most commonly used MND specific disease measure, the ALSFRS-R, to the generic EQ-5D-5L measure with an acceptable level of accuracy which can address some of these limitations, with OLS regression providing the best fit to the observed data. Mean health utility of patients in the TONiC-MND dataset was 0.57 (n=595). Health state utility decreases (from 0.76 to 0.50

using Kings ALS staging and 0.71 to 0.25 using MiToS staging) and health state costs increase (from £1,096 to £3,311 using Kings ALS staging and from £1,115 to £2,899 using MiToS staging over a 3-month period) as disease severity increases. Edaravone is associated with a high incremental cost-effectiveness ratio (ICER) estimate of £1,423,985 per quality-adjusted-life-year (QALY). The cost of the drug, and the significant drug administration costs, both significantly contributed to this estimate. This estimate was also sensitive to assumptions regarding treatment effectiveness, treatment initiation and stopping rules, and transition probability sources used. The economic evaluation of edaravone highlights some of the challenges that may face other potential MND treatments.

Conclusions

Few health economic studies have been published in MND. This thesis adds to the limited evidence base by providing key information on parameters which are essential in performing health economic analysis. This evidence is provided according to well accepted disease staging models and future research should take these frameworks into account when designing studies. Further understandings of MND subgroups may help the development of treatments for MND. This thesis identifies challenges facing the assessment of new treatments for MND and provides new information, including the use of appropriate health economic methods, which can be used to reduce the high levels of uncertainty that will likely be associated with assessments of these new treatments.

Chapter one

Introduction

Motor Neurone Disease (MND) has a devastating impact on those who are diagnosed with this fatal condition and on those who care for people with MND [1]. Limited treatment options exist, and research continues to find a cure or treatments that can halt disease progression [2]. This thesis focuses on MND in terms of the health economic considerations of new potential treatments for the condition. The thesis is composed of several investigative chapters, which focus on presenting different types of evidence which can be used to inform health economic evaluations of MND treatments. This evidence was generated by the collection and analysis of empirical data and application of relevant health economic methods.

This chapter provides the background to both MND and the fundamental aspects of health economics, with a focus on health economic principles commonly used in health technology assessments (HTA). It begins with key aspects of the condition in terms of its epidemiology, risk factors, diagnosis and current treatment options. It also highlights the impact on those who live with the condition and their caregivers. This provides the backdrop to the thesis and highlights the need for the work that will be presented in the chapters that follow.

There have been studies which describe the condition [3,4], and its associated symptoms, but fewer studies have reported empirical evidence to inform health economic evaluations of treatments for MND or have carried out a health economic evaluation of potential MND treatments [5]. The research in this thesis was motivated by the desire to add to this limited evidence base. This chapter outlines the research undertaken in the thesis. It introduces some of the key themes and relevant considerations that run throughout the thesis. It also details the specific aims of the thesis. These were:

- Highlight the current evidence base of health economic evidence in MND populations, detail the methodology used in the identified studies and provide a narrative on areas of uncertainty
- Provide a statistical link from a commonly used MND disease-specific measure to the preference-based EQ-5D-5L measure

- Present health state costs and utilities by accepted MND health staging systems from a UK perspective
- Estimate the clinical and cost-effectiveness of edaravone, a new potential treatment for MND, from a UK health payer perspective. In addition, provide a narrative on the likely challenges that new treatments for MND will face in demonstrating cost-effectiveness

These aims along, with the objectives are described in more detail later in this chapter in section 1.7.

1.1 Principal data sources used in this thesis

Chapters in this thesis make use of several key data sources. These datasets are described below.

Trajectories of Outcome in Neurological Conditions *(TONIC)* study

TONiC is a large longitudinal study into the factors that influence quality of life in people with MND in the UK [6]. The TONiC study included any person with MND, as it aimed to include people from across the MND severity spectrum at various stages of disease progression. It is comprised of many questionnaires, covering a wide range of aspects of living with MND. This thesis uses relevant questionnaires which cover health economic aspects. This involved people with MND responding (or their carers responding on their behalf) to questions regarding physical and emotional wellbeing, as well as economic impacts. Several research papers have already used this resource [7,8] with more studies planned. Databases such as TONiC will be valuable in adding to the limited evidence base as it contains a depth of disease-specific information. This thesis benefited from the use of baseline data from the TONiC study, in particular chapters 3,4 and 5. The TONiC study is still ongoing and should prove to be a valuable source of data for quality of life research in MND. This is particularly true when longitudinal data has been collected in sufficient numbers, which can investigate how quality of life and clinical outcomes change over time.

PRO-ACT dataset

Another database used in this thesis is the Pooled Resource Open-Access ALS Clinical Trials (PRO-ACT) database [9]. The usefulness of this resource is clear as it combines pooled patient observation data from 23 phase II and phase III trials and one large observational study in MND, and these numbers are expected to increase over time. The dataset includes trials which were carried out across various countries. It provides longitudinal data in key clinical areas which allows insights into outcomes (such as survival) over time. It is publicly available, making it accessible to researchers. This database is used in chapter five, utilising this resource to match patients in this database to the strict inclusion criteria of the pivotal edaravone trial (see next section 1.4 for more information on edaravone) [10].

1.2 Motor Neurone Disease

Motor Neurone Disease (MND), also known as Amyotrophic Lateral Sclerosis (ALS), is an incurable neurodegenerative condition, which leads to a progressive loss of motor function and eventual death [11]. The terms MND and ALS are sometimes used interchangeably, since around 90% of MND cases are the mixed ALS form which is also referred to as Progressive Muscular Atrophy (PMA). The other 10 percent of MND cases are terms as Primary Lateral Sclerosis (PLS), and these MND cases tend to have a slower rate of progression [12]. In MND the nerve cells (motor neurones) stop transmitting signals to the muscles in the body, resulting in muscle stiffness and wastage. This leads to a loss of loss of movement in arms and legs and other body regions, impacting the ability to carry out everyday tasks. The condition is characterised by large levels of heterogeneity across patients, including differing rate of disease progression, adding to the complexity of care [13].

Epidemiology and aetiology

MND is associated with a life expectancy of around 3 years from symptom onset [14]. Prevalence estimates vary, with an estimated incidence rate of around 3 per 100,000 in the UK [15]. There are an estimated 4000 to 5000 people living with MND in the UK [16]. With this level of prevalence, MND can be considered a rare disease and the implications of this in relation to this thesis are discussed in detail in section 1.6. The number of people living with MND is expected to increase as life-expectancies continue to rise. The cause of the disease is

unknown and research is continuing in this area to better understand the underlying mechanisms which play a role in MND, with certain environmental and lifestyle risk factors identified such as smoking, age or exposure to certain substances [17]. Only around 5%-10% of MND is believed to be familial (inherited), with the majority termed as sporadic MND [18]. The mean age of MND onset is mean age at onset is between 58–63 years, with the condition mainly affecting those between the years of 50 and 70, however MND onset can occur at any age [19].

MND consists of several subgroups, depending on which types of motor neurones are affected first by the condition, although symptoms between subgroups can overlap particularly as the disease progresses. Amyotrophic lateral sclerosis (ALS) is the primary subgroup with around 80% of MND patients with this diagnosis, where symptoms tend to start in the hands and feet, however the term ALS is commonly used in the U.S to describe all MND types [20]. Progressive Bulbar Palsy (PBP) makes up around 20% - 30% of those with MND, where the muscles first affected are those responsible for talking and eating [20]. Rarer forms of MND include Progressive Muscular Atrophy (PMA) and primary lateral sclerosis (PLS). Prognosis can differ depending on the site of symptom onset, with bulbar onset associated with poorer prognosis [21]. MND is a highly heterogeneous disease and predicting accurate survival times using various prognostic factors can be difficult [22,23].

Diagnosis

Diagnosing the condition is difficult, as some of the symptoms can be similar to those experienced in other neurological conditions [24]. Symptoms can be mild at the beginning of the disease. Therefore, a diagnosis can take time to confirm and can typically take around a year [25]. Tests must be done to rule out other possible conditions. The El Escorial criteria can be used to help diagnose MND (allows various levels of diagnostic certainty: definite, probable, possible and suspected) and the criteria is often used in clinical trial eligibility. Timely diagnosis can help initiate early interventions, which can improve clinical outcomes [26].

Any voluntary muscle can be affected by the condition. Cognitive impairment can also occur, but many people with MND do not experience substantial deterioration in cognition, although it is more common in the later stages of the disease [27]. MND impacts on the ability to

communicate when the muscles responsible for speaking and breathing become affected [28]. The condition can also have a major impact on carers, particularly at later stages of the disease, when assistance is needed to carry out everyday tasks [29].

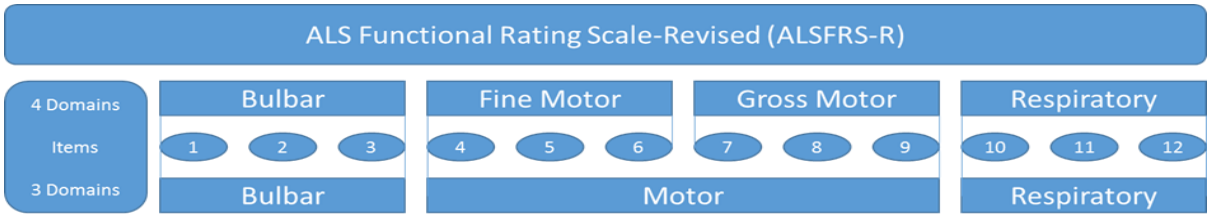
1.3 Clinical staging and disease-specific measures in Motor Neurone Disease

Measurement of disease progression in chronic diseases like MND is important. It allows better understanding of how the disease is impacting on people with MND and their caregivers [30]. This can inform discussions regarding treatments and help advise on adaptions. Measures used to record disease progression in any condition should capture important clinically meaningful changes to patients and be sensitive to these changes along the disease course. These clinically meaningful changes may also be economically meaningful, with changes to treatment need and resource use. Disease-specific measures can also be used to inform clinical staging systems, which identifies unique health states that patients may be in across the course of the disease.

Amyotrophic Lateral Sclerosis Functional Rating Scale- Revised (ALSFRS-R)

The ALSFRS-R is an MND specific questionnaire and the most used measure of clinical effectiveness in clinical trials of treatment for MND [31]. It is comprised of 12 questions with domains including bulbar (speech, salivation, swallowing), fine motor (handwriting, cutting food, dressing/hygiene) gross motor (turning in bed, walking, climbing stairs) and respiratory (dyspnoea, orthopnoea and respiratory insufficiency). Each question has five possible responses which vary in level of disease severity, with a score for each item ranging from 0 (lowest functioning) to 4 (no functional loss). Therefore, the full index score for the ALSFRS-R ranges from 0 to 48. A structure overview of the ALSFRS-R measure can be seen in figure 1.1.

Figure 1.1: Structure of ALSFRS-R



The ALSFRS-R is relatively simple to complete and provides information on how the disease impacts functioning in various body regions. It can also capture whether gastrostomy or tracheostomy has been carried out. The measure, whilst commonly used, is not without criticism. There has been concerns about the sensitivity of the measure and the usefulness of the full index score, as not all changes in ALSFRS-R items mean the same in terms of disease progression or prognosis [32]. Some have advocated the development of a new measure, amendments to the current ALSFRS-R measure, or more use of the measure's domain rather than the index scores as they believe that to be more clinically relevant. Some studies have also highlighted the value of using the slopes of ALSFRS-R domains, suggesting that they provide better statistical fits to prognostic models that the full ALSFRS-R index slope [32-34]. One study, informed by a survey of MND clinical experts and researchers, suggested that a 20% decrease in ALSFRS-R decline is a clinically meaningful change [35].

Clinical staging and MND

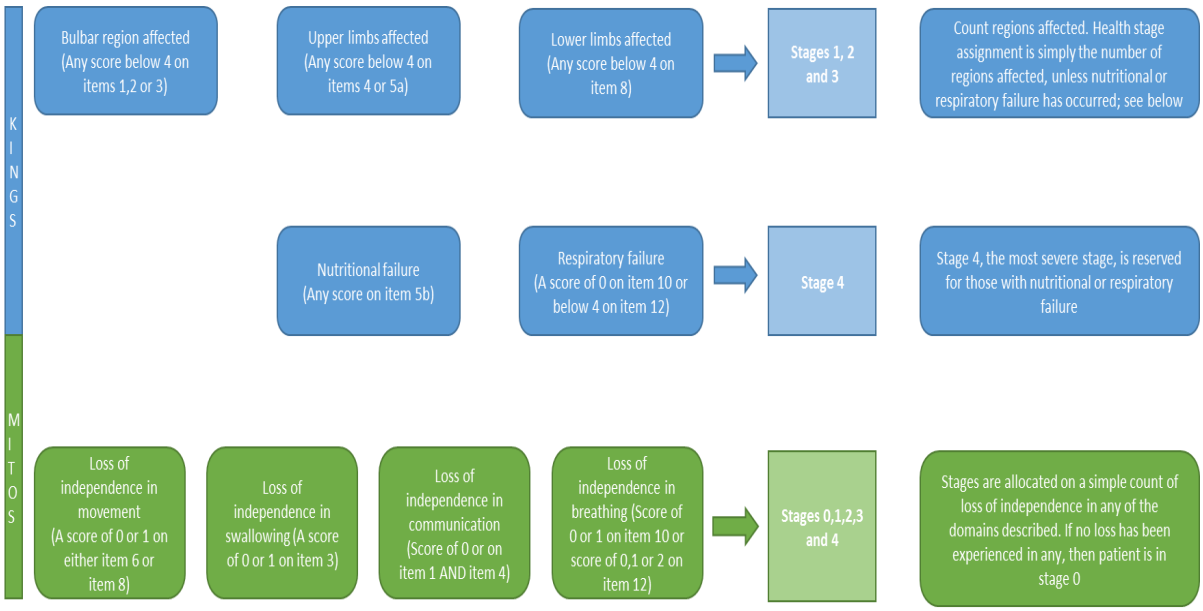
Clinical staging involves the identification of important and mutually exclusive descriptions of health states within a disease. In such staging, all the disease population should be assigned a stage. The use of clinical staging in health economic evaluation is increasingly common [36,37]. A major advantage of using clinical staging in MND is that it can provide useful information on important clinical milestones, which may not as clear when only using results from a outcome such as the ALSFRS-R index score for example. Clinical staging can allow differences in disease progression (as determined by transitions from better health states to worse health states) to be detected in clinical trials for new treatments, even when these trials are short in duration. Often, trials in MND are typically, through design, not long enough to provide enough information on differences in overall survival, further highlighting the usefulness of the use of clinical staging systems in clinical trials for MND. Clinical staging also allows study of how costs change as disease progresses and treatment demands increase.

A suitable staging model for MND should identify key clinically important distinct health stages which capture the natural progression of the condition and can be easily applied to trial data. The El Escorial criteria provides guidelines for diagnosing MND, based on patterns of

disease spread, but is not a staging system [26]. In Motor Neurone Disease, there has been numerous proposed clinical staging systems, which focus on certain characteristics and symptoms of disease progression.

While there have been several proposed systems, the main clinical staging systems in current use include Kings ALS staging and the Milano-Torino (MiToS) staging systems [38,39]. While these staging systems have been used to monitor disease progression, they are not used to diagnose the condition, and are not necessarily used to define a clinical stage at diagnosis. The Kings ALS system focuses on the number of body regions which have been affected and whether gastrostomy or non-invasive ventilation has been required. The staging of patients in this system relies on a clinician examination. The MiToS is focused the loss of independence in certain domains. The MiToS system is based directly on responses to items from the ALSFRS-R measure. The Kings staging system can be also estimated from responses to items of the ALSFRS-R, with a 92% level of accuracy, by using an algorithm [38]. The ability to link both of these systems to the ALSFRS-R, either directly with the MiToS system or indirectly with the Kings system, is important as the ALSFRS-R measure is commonly used in clinical trials. A brief overview of the Kings and MiToS staging systems, and their relationship to the ALSFRS-S, can be seen in figure 1.2.

Figure 1.2 – Kings and MiToS Staging models



A study presenting a comparison of the Kings and MiToS staging systems showed that the two systems can complement each other, rather than both producing the same types of evidence [40]. The study highlighted that the distribution across stages differ between the systems. The Kings system has a higher resolution in earlier timepoints in the disease, whereas MiToS had higher resolution at later timepoints. This comparison study recommends the use of both systems to describe the extent of disease progression in MND. More recently, another staging system has been proposed called the 'fine til 9' or FT9 system [41]. The FT9 staging system is based directly on the ALSFRS-R (like the MiToS staging system). Stages are defined by the number of ALFSRS-R domains which have a score of 9 or less (maximum score for each domain is 12).

Clinical staging brings a range of benefits in its use in MND clinical practice. It correlates with key functioning decline measures and helps to account for the heterogeneity of the condition [42]. It also helps to describe health-related quality of life and costs of the condition at different stages. Discussion and debate continue within the MND community on how to best monitor and describe how the disease progresses.

1.4 Current treatments, and new potential MND treatments (such as edaravone)

Current treatment options

As is the case with many rare diseases, treatment options are limited for MND. Current treatment for MND in the UK consists of care delivered by a multidisciplinary team, which includes a range of services such as specialist nursing, diet planning, physiotherapy and speech and language therapy. Respiratory, psychological, and palliative care services are also offered [43]. This type of care has been shown to increase life expectancy and quality of life [44]. Weight loss is common in people with MND, as feeding becomes problematic, and a gastronomy may be performed (insertion of a feeding tube) to aid with nutrition. Pain is also experienced by many MND patients and may need to be managed [45]. Respiratory failure is the main cause of death in MND, and non-invasive ventilation (NIV) has been shown to prolong survival [46]. Tracheostomy ventilation (TV) can also form part of the treatment pathway in the later stages, with careful considerations on the impact and the appropriateness of TV [47]. NICE clinical guideline 42 outlines clinical guidance for the treatment of MND in the NHS [48]. This guidance recommends that certain prognostic factors that are

associated with shorter survival times should be taken into account, when planning care, including bulbar onset, weight loss, poor respiratory function, older age, lower levels of functioning and shorter times from symptom onset to diagnosis. The guidance also recommends that multi-disciplinary care should be tailored to each individual patient's symptoms, which can vary over the disease course. The guidance also explains that cognitive function and the need for psychological support should also be monitored over time in addition to considering the communicative functioning of the patient, as this may become affected due to MND. The importance of end-of-life planning is also highlighted.

Only one disease-modifying drug (riluzole) has been licensed in the UK for treating the disease. Riluzole was shown to extend survival in clinical trials compared to placebo [49]. The National Institute of Health and Care Excellence (NICE) recommend riluzole for use in the NHS based on trial evidence that suggested it extended tracheostomy-free survival by between 2 and 4 months. However recent research has demonstrated that the majority of the extended survival time associated with riluzole use is spent in a severe health state [50]. The NICE guidance on riluzole also states the likely cost-effectiveness estimates were above £30,000 per QALY gained (the upper limit of the threshold range used by NICE) with most plausible estimates between £34,000 and £43,500. However, it approved its use when considerations of the severity and short life-expectancy associated with the condition along with the value placed on tracheotomy-free survival by patients were taken into account.

As this thesis is concerned with providing evidence which aids health technology assessments of new MND treatments, it is important to note the current environment in terms of available and potential treatments on the horizon. Riluzole was approved for treating MND by NICE in 2001, being the first, and to date only, drug treatment with a marketing authorisation for the condition in the UK. There have been many clinical trials since then involving a range of drugs, but none provided robust evidence of clinical benefit [51].

Edaravone – a potential new treatment option

More recently, in 2017, edaravone was approved by the Food and Drug Agency (FDA) in the United States. Edaravone is a free radical scavenger, which had also been approved for treatments such as acute stroke in some countries such as Japan, although not in Europe or the US. The mechanisms by which edaravone may slow down the functional decline of MND

is unknown, but it is thought that oxidative stress may be one of the mechanisms involved in MND, which edaravone may reduce [52]. An initial edaravone phase III trial failed to show a statistical difference between the intervention and placebo group [53]. A post-hoc analysis of this trial showed that edaravone may work better in patients who were in earlier stages of the disease [54]. This resulted in another edaravone trial with patients who had less severe disease (MCI186-19). The inclusion criteria for the MCI186-19 trial were strict [55]. Patients were required to have had MND symptoms begin less than two years prior to the trial, a high forced vital capacity and no respiratory deficit as measured by the ALSFRS-R (see section 1.4 for more details on this measure). These criteria have been criticised for representing only a small subset of MND patients. A study by Hardiman et al. stated that if the edaravone inclusion criteria were applied to a general register of MND patients, only 7% would have been eligible for the trial [56].

The comparative study duration of the edaravone trial (MCI186-19) was limited to 6 months, after which point those on the placebo arm were permitted to receive edaravone treatment. The approval of edaravone by the FDA was based on clinical evidence presented in the restricted population trial which showed that edaravone slowed progression, as measured by the ALSFRS-R (see section 1.4 for a full description of this measure), by around 33% compared to standard care, with the placebo group ALSFRS-R score declining by 7.50 compared to a 5.01 decline in the edaravone group. Therefore, the mean difference between the groups was 2·49 (SE 0·76, 95% CI 0·99-3·98; p=0·0013) in favour of edaravone [55]. This difference was statistically significant. The FDA, however, approved edaravone for use in the full MND population, despite no evidence it provides a clinically meaningful benefit to those with more severe disease.

The short duration of the MCI186-19 study [55], and the relatively low disease burden in the trial cohort, meant that differences in key clinical outcomes could not be assessed as no deaths were observed in either group and no patients required ventilation or gastronomy by the 6-month mark. While the decline in ALSFRS-R score was slower in the edaravone group, long-term trial data was not presented, so the impact of edaravone on overall survival was not investigated. Observational studies carried out since the FDA approved edaravone's use in the US and other locations suggests that, when used among the wider MND population, there is likely to be little difference between the edaravone and placebo group [57,58]. The U.S list price for edaravone results in a yearly drug cost of around $145,000 (based on 2017 price:

converted to GBP equals to £110,637). Another important aspect of edaravone treatment is the burdensome administration regime. Edaravone is given via intravenous infusion each day for two weeks in the first month of treatment, with infusions given for 10 days over two weeks in each subsequent month. There is considerable burden on patients, with most administrations taking place in clinics, requiring travelling and time commitments [59]. The impact (or disutility) of these aspects of edaravone treatment in MND has not been reported but should be considered. Long term data on adverse events are also not yet available.

In May 2019, the manufacturer of edaravone withdrew its submission to the European Medicines Agency (EMA). This was a result of the Committee for Medicinal Products for Human use (CHMP) identifying several issues with the evidence base including the short duration of the clinical trial (the EMA usually advocates trials of at least 12 months), small numbers of patients enrolled and the lack of information on effect of edaravone on survival or other important clinical outcomes [60]. The committee also noted that when patients in the control arm of the trial were switched to edaravone, there was no noticeable treatment effect in those who switched. In addition, the committee noted that there were imbalances in terms of baseline disease severity, with those in the edaravone group with less severe disease on average. The committees report states that this may have influenced trial results.

Other potential treatments

Investigations into potential new treatments for MND are ongoing and there is hope for more treatment options to become available [61], some are highlighted briefly in this section.

The Motor Neurone Disease Association maintains a list of potentially promising new treatments which are currently being studied in clinical trials [62]. Potential treatments which may slow down the progression of MND include reldesemtiv, a fast-skeletal muscle troponin activator (FSTA). A phase II trial of reldesemtiv failed to meet its primary (slow vital capacity: SVC) or secondary (ALSFRS-R) endpoints at 12 weeks for specific treatment groups defined by dose strength [63]. A post-hoc analysis of this trial using the pooled data (all dosing groups combined) however did highlight a 25% decrease in the decline of the ALSFRS-R from baseline to 12 weeks ($p=0.01$). The greatest ALSFRS-R benefit seen in the gross motor domain (which covers turning in bed, walking and climbing stairs), and this decrease in decline was statistically significant at each dose compared to placebo. This post-

hoc analysis also showed a 27% reduction in SVC, although the p-value associated with this was 0.10. Further clinical trials of reldesemtiv in MND are planned.

There are also several other potential treatments under review which aim to slow down the progression of MND. These include CuATSM (Copper ATSM), which may work by providing copper cells to damaged mitochondria, potentially improving respiratory and cognitive function and slowing down progression. A phase II trial is ongoing after an earlier phase 1 trial showed some promise [64]. Another potential treatment is ibudilast, an anti-inflammatory drug. A Phase IIB/III trial is currently ongoing after an earlier phase II study showed that some patients who took ibudilast did not experience a decline in ALSFRS-R score [65]. Again, like in the case of edaravone, there is a belief that treatment effects of the drug may be higher in those with less severe disease, and those included in the ongoing trial were those with milder MND [66]. In contrast, AMX0035 (combination of sodium phenylbutyrate and tauroursodeoxycholic acid that work to minimize cellular mechanisms linked to cell death in ALS) is a potential treatment that may work better in those with fast progressing disease, with a phase II trial ongoing [67].

Recent advancements in gene therapies offers a potential new aspect of treating MND, particularly those with MND which has mutations in SOD1 or C9orf72 genes (however there are a large range of gene mutations associated with different forms of MND and the proportion of MND caused by SOD1 and C9orf72 gene mutations makes up a minority of the full MND population) [68]. Gene therapies are experimental techniques, which aim to treat a disease by modifying the patient's genetic material, this is most commonly attempted by introducing a health copy of the affected gene into the patient's cells [69]. One such potential gene therapy is tofersen, which was shown to have good tolerability in a phase 1 trial, which a phase 3 trial now ongoing [70]. Tofersen is artificially manufactured DNA designed to bind to SOD1 mRNA, which reduces levels of SOD1, potentially slowing progression. Research continues in this area to find uses of gene therapy for a broad range of MND caused by various genetic mutations. Recent approval of a gene therapy in spinal muscular atrophy (SMA) in children is a promising development [71]. Successful development of effective gene therapies for MND offers potential cures for the condition, which could lead to significant health benefits although the costs of such treatments are likely to be highly expensive which may lead to difficultly in these treatments being recommended for use in the NHS.

The above-mentioned treatment list is not exhaustive, but does give an indication that new treatments may not be too far away. As can be seen from the brief discussion on potential new treatments in the current pipeline, there are several different types of treatments under review. Each of these have different mechanisms of action and may provide a range of relevant benefits (varying in their desirability/utility). Each will also be subject to challenges in demonstrating their value and long-term effects (more on this discussion can be found in section 1.5). The next section of this chapter goes into more detail on the commonly used outcome framework in MND.

1.5 Health economics in Motor Neurone Disease

Healthcare systems, such as the NHS, provide health services usually under the constraints of a fixed healthcare budget. This inevitably limits the number of services that a health services can offer. Therefore, choices need to be made as to which health interventions to fund. Each intervention which gets funding means that another potential intervention cannot be funded. The alternative option forgone is known as the opportunity cost. In general, healthcare decision makers will want to ensure that the choices made provide levels of improved health outcomes that would not been achieved using the resources (usually money) elsewhere. Health economics can be used to estimate the desirability or value of each healthcare choice in terms of the health benefits provided. The discipline therefore provides key analysis to aid healthcare decision-makers.

Health economics

Health economics is a sub-discipline of economics which has seen increasing prominence in healthcare provision and decision-making. The subject encompasses a broad range of topics such as how health is valued (including who should value it), factors which influence health, demand and supply of healthcare, and market equilibrium [72]. Like in other fields of economics, there are large demands on scarce resources. Health economic analyses play a central part in deciding whether a new intervention should be funded, knowing that this decision means less resources for other healthcare provision. Health economic analyses need to be accurate and use appropriate methods in order to provide a robust framework, so that their results can be interpreted with an acceptable level of confidence and that the risk of

decision error is reduced (risk of making an incorrect decision). A framework in this sense is a conceptualisation of a set of rules or assumptions. A health economic framework's robustness is seen in its ability to capture all important aspects of the clinical and economic elements of the condition for which the intervention is intended to treat. This also relies on the inputs into the framework, and the sources informing them. Therefore, these sources individually contribute to the overall robustness of any health economic framework.

Health economics is usually seen as a branch of normative economics, which involves analysis being guided by value judgements regarding the relative desirability of different outcomes [73]. This differs from positive economics, which outlines the relationships that exist between variables and predict outcomes on this basis [74]. Health economics can also offer some insights into positive economic analysis. Normative economics relies on subjective judgements, there evitability will be debate within the field of health economics on the relevant scope of the discipline (what are the "rules" and relevant considerations). The aim of health economic analysis is to choose the health interventions/policies that will maximise utility. Utility, in this context, can be thought of as the value or satisfaction derived by different states of the world. The main paradigms of normative analyses in health economics are rooted in welfarism and extra-welfare theory.

Welfarism

Welfarism presents how society values outcomes in terms of their desirability [75]. These outcomes are termed as utility which is achieved by individuals. Under welfarism, it is assumed that individuals affected are the best placed to value their own utility. Pareto efficiency is a fundamental part of welfarism, which states that the pareto efficiency point is a state of the world that no individual's utility can be improved (pareto improvements) without reducing the utility of another [76]. Pareto efficiency can be theoretically achieved with various given sets of initial distributions of utility across society. Comparisons between states in which some individuals' utility is better at the expense of others utility are deemed not possible or of limited value. Welfarism does not explicitly consider the issue of prior distributions of utility, nor does it offer a framework for addressing equity or ethical redistribution of utility [77]. In welfarism, social welfare (the value society places on a set of outcomes) is the sum of individual utility. A more expansive approach is that of extra-welfarism which rejects individual utility being the only relevant outcome in an evaluation.

Cost-benefit analysis is used in welfarism, where all costs and benefits are expressed in monetary terms. Cost benefit analysis allows the comparison of two or more treatment options in terms of net monetary benefit (which is the difference in monetary benefit of an intervention minus the costs of that intervention). Valuations of benefits can be derived through willingness to pay surveys or discrete choice experiments (DCEs). These methods estimate the value of certain attributes/outcomes of an intervention. Cost benefit analysis can be difficult to carry out in health economics, as it can be difficult to attach monetary value to certain health outcomes, although it may be used for assessing the value derived from reduced waiting/travel times in healthcare, or valuing the benefits of a different dosing method/frequency.

Extra-welfarism

Extra-welfarism (or non-welfarism) expands the scope of factors considered relevant in welfarism [78]. This approach allows both individual utilities and other non-utility parameters to form part of decision-making in relation to optimal use of resources to maximise societal welfare. These non-utility considerations may include the characteristics of the group which is receiving the intervention or the impact of an intervention in terms of individual's capabilities, well-being, or freedoms. Other relevant considerations may include the distribution of health or incremental health gains and factors such as caregiver burden and patient satisfaction derived from the process/type of healthcare. Influential work by Sen helped to promote this expansion of the evaluation space in health economics in this discussion of the capabilities approach [79]. Sen argued that utility should focus on individuals' freedoms and functioning, with the aim to enhance the quality of life they are able to achieve. This is a broader definition of benefits, moving away from thinking about individual utility to maximising health. The prominent measure used in analysis which aims to maximise health is the quality-adjusted life year (QALY), a combination of life years and quality of life gained from different healthcare options [80]. Cost utility analysis is used in extra-welfarism analysis, which estimates the incremental cost per QALY gained. Extra-welfarism also allows for a weighting to be placed on outcomes based on prior preferences or ethical considerations. Within this framework, decision-makers can decide the relevant value of outcomes, informed by the analyses of health economists, experts, public opinion and other factors. Cost-utility analyses allows comparisons to be made across different disease areas and is the analysis which NICE recommends in manufacturer submissions. This thesis

will focus on cost-utility analysis, and the inputs required for this analysis, for this reason. Extra-welfarism allows discussion to move away from the restrictions of pareto efficiency. A detailed discussion of the similarities and differences of welfarism and extra-welfarism is offered by Brouwer et al [81]. Debate still exists between health economists on the merits of both approaches in terms of determining the relevant considerations when deciding on the choices between different states of the world in terms of societal desirability [82,83].

A key output of applied health economics is economic evaluations, which bring together several aspects mentioned in the previous paragraphs. Health economic evaluations are described below along with reference to health economic considerations which may apply to the assessment of new treatments for MND.

Health economic evaluations

Health economic evaluations are concerned with assessing new interventions in terms of their value for money, often under the constraints of a fixed healthcare budget. Decision makers are faced with the task of selecting which treatments to provide. To compare the value of new treatments we need to contrast the various outcomes and costs of potential healthcare interventions in relation to current standard of care treatments used in clinical practice. We also need to consider the impact of recommending one treatment as it results in reducing funds for other healthcare expenditure, opportunity cost.

Health economic evaluations focus is on the "cost-effectiveness' of new potential health interventions. Cost-effectiveness presented as cost-utility analysis combines both the clinical effectiveness (utility gain created) of an intervention with the costs of providing it. Clinical effectiveness is usually considered in both gains in survival and improvements in health-related quality of life. Utility (value derived from a range of health states) is the focus in health economics. This is assumed to be captured in the QALY calculation. Whether to expand the scope of health economic evaluations beyond those captured in the QALY measure, or whether the QALY is the best measure to capture utility, is part of a wider debate [84,85]. This thesis will focus on direct health benefits, due to the type of data available and the requirements for health technology assessment (HTA) set out by the National Institute for Health and Care Excellence (NICE) in England and HTA agencies in other nations, although discussion is provided on certain beyond the QALY measure which may apply to MND in

regard to reimbursement decisions (for example those taken by NICE) when assessing new treatments for the condition.

Health utility is usually measured through the use of generic preference-based questionnaires with health domains and can be applied across different health conditions. Utility values are calculated (based on general population preference studies) for all possible combinations of responses to these questionnaires, with each unique response resulting in a different utility value [86]. The most commonly used generic preference-based measure of health in economic evaluations in the UK (and most of Europe) is the Euro-Qol EQ-5D, which covers five domains of health (mobility, self-care, daily activities, pain, and anxiety/depression) [87]. The EQ-5D has several national utility datasets, including datasets for the UK (using preferences of various health states elicited from a representative sample of the UK population). Other examples of generic preference-based measure include the Health Utility Index (HUI) [88] and the short-from 36 (SF-36) [89].

Two aspects of clinical effectiveness, extensions to life and improvements in health-related quality of life, are captured in the quality-adjusted-life-year (QALY). While the use of the QALY as the measure of utility is not without its critics and limitations, it does provide a systematic way of valuing health gain across conditions. The QALY is calculated by multiplying the difference in survival and quality of life provided:

QALY = life years gained x quality of life in those life years

Example: A current treatment option for a condition provides a life extension of 5 years and an average health utility of 0.6 for those five years. Combining these two aspects yields a QALY gain of 3 (5 x 0.6 = 3). Another treatment offers a life extension of 10 years with an average health utility of 0.6 for those years, therefore a QALY gain of 6. Incremental QALY gain for the new treatment is 3 QALYs.

The cost-effectiveness estimate of a treatment is normally presented as a cost per QALY gained, compared with current treatments, and shown as an incremental cost-effectiveness ratio (ICER). All relevant associated costs of a treatment should be considered, including those relating to drug acquisition, administration and costs relating to adverse events, among others. The relevance of each cost is determined by the perspective of the payer. Costs

included in economic evaluations in the UK tend to be those relevant to healthcare providers, which in the case of this thesis is assumed to be the NHS. Again, a wider debate exists on whether indirect costs should be considered, for example those incurred by the patient or caregiver or productivity costs [90].

The incremental cost-effectiveness ratio (ICER) is the incremental cost divided by the incremental benefits and can be calculated as below (where treatment A is the new treatment and treatment B is the comparator treatment)

$$ICER = \frac{\text{total costs treatment A - total costs treatment B}}{\text{(total QALYS treatment A - total QALYs treatment B)}}$$

NICE and health technology assessment (HTA)

Within England, NICE has a remit from the department of health to assess potential new treatments for use on the NHS. The establishment of NICE in 1999 was in part to eliminate the "postcode lottery", which meant that the availability of some treatments varied by regions of the country. NICE uses a cost per QALY approach when assessing new treatments in terms of the value for money they offer. The ICER range NICE normally considers acceptable per QALY gained is between £20,000 and £30,000 [91]. NICE sets out the relevant considerations in economic evaluations in UK healthcare provision of new drug treatments in its reference case [92]. This thesis aims to provide evidence which can be used to satisfy key elements of this reference case. It should be noted that NICE reference case also allows considerations of benefits that are not captured within the QALY, although it does not state explicitly what sort of benefits can be considered under this stipulation. NICE also allows consideration of new treatments in terms of its innovation, again the measure of innovation is ambiguous in NICE appraisals.

The NICE reference case also states that the time horizon within an economic evaluation should be long enough to capture all relevant benefits and costs of competing interventions. This usually results in a lifetime horizon (which outcomes are accrued until death) being the most appropriate in analysis which estimates impact of health interventions.

Clinical evidence informing the effective of treatments normally comes from clinical trials, which only provide evidence for the length of time the trial runs for. Health economics is compatible with methods which can be used to extend the analysis of costs and benefits beyond those observed in a clinical trial. These methods involve extrapolating outcomes well into the future. Examples of extrapolating beyond trial data include fitting standard parametric distributions, individual simulation models and Markov modelling. Regardless of the methods chosen, costs and QALYs which occur in the future need to be discounted to estimate their "present value" and reflect the fact that benefits gained in the near future are valued higher than those gained in the long term [93]. The same logic holds for costs, those occurred in the future are considered more desirable than costs occurred up front (inflation is also a consideration for discounting). The current NICE reference case states a discount rate of 3.5% should be applied to costs and benefits occurred in the future. The choice of discount rate can significantly impact on the estimated cost-effectiveness of treatments, especially those which have high upfront costs with most of the benefits occurring in future years. Examples include one-off new gene therapies. NICE also states that in cases were treatments restore those with severe or terminal disease to full health (or near full health) a discount rate of 1.5% may be appropriate [94]. Drug manufacturers, as part of their submission to NICE, provide an economic model (normally a cost-utility model) which uses parameters and analysis set out in the NICE reference case. The economic model is a key component of any NICE appraisal. A summary of the NICE reference case can be seen in table 1.1.

Table 1.1 – NICE reference case (adapted from the NICE guide to the methods of technology assessment [91])

Health technology assessment element	**Details**
Defining the decision problem	Outlines the assessment in terms of population(s) to be considered (including relevant subgroups), intervention, comparators, outcomes and other relevant considerations.
Relevant comparators	Defined by the current treatment options used in the NHS. These may be treatments which have been previously recommended by NICE. In general, relevant comparators are those who form part of routine care and whose use would continue unless displaced by the intervention under appraisal. NICE committees may also relevant

	comparators after considering a fully incremental analysis.
Perspective - outcomes	Direct health benefits for patients. Where relevant, carer health benefits can also be considered.
Perspective - costs	Costs paid by the National Health Service (NHS) and Personal Social Services (PSS)
Evaluation type	Cost-utility analyses with fully incremental analyses.
Time horizon	Long enough duration to capture all important changes in costs and outcomes. In many evaluations this will be a lifetime horizon.
Evidence synthesis	Systematic review
Measuring and valuing health	Health outcomes expressed in quality-adjusted life years (QALYs). The EQ-5D is NICE's preferred of health-related quality of life in adults.
Source of preference data (HR-QoL)	Reported directly from patients and. where relevant, carers.
Equity considerations	QALYs are considered to be of equal weight (value) regardless of the characteristics of those who receive them. There are some exceptions to this component, for example NICE's end of life criteria (proposed to be replaced) or the proposed severity modifier.
Resource use and costs	Prices relevant to the NHS or PSS.
Discounting	Currently 3.5% annually for both costs and outcomes

Health economics and MND

As mentioned earlier in this chapter, NICE recommended riluzole in 2001 for MND. This recommendation was based on analysis which presented a most plausible ICER range between £34,000 to £43,500 per QALY gained. This was above the range normally considered cost-effective but took into account other considerations (see opening section of this chapter [95]. In 2009, NICE introduced its criteria by which a higher willingness-to-pay

threshold (up to £50,000 per QALY gained) can be applied to life extending treatments at the end of life (NICE's end of life criteria). Although some research in this area shows that people may not value treatments which extend survival at the end of life as highly as the increased threshold would suggest [96]. This additional weighting applied to health gains in conditions which are considered to have low life expectancy could be seen through the lens of an extra-welfarism framework, which allows other considerations to enter the evaluation process. For a new treatment to meet these criteria, people with the condition should normally be expected to live less than 2 years with the current standard of care. In addition, the treatment should extend life by more than 3 months. In the context of MND, with its life expectancy at just over 2 years, treatments would unlikely meet these criteria, although NICE committees have shown some flexibility in its application of this criteria when conditions have life expectancies just above 2 years. It should be noted that treatments for later stages of MND, as defined by either the Kings or MiToS system, or subgroups with fast progressing disease may meet the criteria [38.39].

NICE also has a highly specialised technologies (HST) programme, which considers rare conditions which are treated in a small number of specialised centres [94]. Treatments which meet the HST criteria can be associated with a significantly higher cost-effective estimates, with a usual acceptable ICER up to £100,000 per QALY gained. The reason that NICE has this program, which can use different methods, is to incentive the development of drugs for rare diseases as it can sometimes be difficult for manufacturers to recoup their investment in drugs (although see section 1.6 for a wider discussion on the debate surrounding the funding of treatments for rare diseases). The acceptable ICER threshold can go up further, to £300,000, if the treatment provides substantial additional QALYs, on average, compared to standard care. Treatments for the full MND population would not meet the HST criteria as set out by NICE as the number of people with the condition would be considered too high (4000-5000), based on the population sizes accepted previously. In addition, the number of specialist MND centres in England is also likely to be considered too many to meet HST inclusion. However, treatments which target specific smaller subsets of MND populations, such as those intended for SOD1 and C9orf72 genes may be considered for HST inclusion as the numbers in these subgroups are likely to be sufficiently small (see section 1.3). These treatments may also require highly trained health professionals to administer and monitor their use, which may only be possible to provide at only a few specialist centres, thus meeting this criteria.

Potential new treatments for MND may face issues in demonstrating cost-effectiveness at traditional willingness to pay thresholds. This is because the recurring costs of MND care can be high [97]. Therefore, treatments which do not cure the condition, but rather prolong survival (sometimes in health states with relatively low utility values), result in these healthcare costs being accrued for longer compared to standard care. Higher background costs associated with condition means a higher QALY gain is needed from a treatment to make it cost-effective. The price of the treatment, which is likely to be in addition to background care in the case of MND, also plays a critical role in determining the chances of it being cost-effective. There has been debate in the literature regarding scenarios like this, including when treatments can be shown to not be cost-effective even at a zero price [98]. However, it is generally accepted that all relevant costs should be included in cost-effectiveness analysis. Further issues can be encountered when the administration costs of new treatments are higher than those used in standard care. This is the case for edaravone, which is administered intravenously, compared to riluzole, which is taken orally, and which has generic versions available. However, future possible treatments which potentially offer a cure, or offer large survival gains in relatively high functioning health states, may not incur significant background care costs but provide high incremental QALY gains.

Relatively few health economic evaluations have been published that consider treatments for MND, compared to the number of such studies in other disease areas. This is likely related to the fact that only riluzole has been approved by the European Medicines Agency (EMA) for treating MND. With the development of new and relevant clinical staging models, there is potential for a greater understanding of how potential new treatments may impact time spent in clinically and economically important health stages (see section 1.4). One example of this is analysis which has applied the Kings ALS staging system to riluzole clinical trial data. In previous analysis, using an older clinical staging system, riluzole was estimated to prolong life across mild, moderate and more severe health stages [49]. Using the Kings ALS staging, however, showed that the increased survival associated with riluzole use was experienced mostly in the most severe Kings stage (stage 4) [50].

1.6 Rare diseases: Implications for decision making

The issue of disease rarity is interesting and challenging when it comes to healthcare provision. The generation of evidence is usually more difficult for treatments indicated for rare conditions and trial data may be limited to single-arm trials with low numbers enrolled. Rare diseases can also be associated with higher levels of heterogeneity, making comparisons with current care hard and adds uncertainty to the extrapolation of results over a lifetime time horizon. There are many rare diseases, with the World Health Organisation estimating that there are between 5,000 to 8,000 [99] Many of these rare diseases have limited treatment options available, although there has been large growth in this area of healthcare in terms of research and development of orphan drugs. A drug can given orphan status by the EMA if it meets certain criteria [100] including:

- that it must intended for a condition that is life-threatening or chronically disabling, and
- the prevalence of the condition must not be more than 5 in 10,000 (or it is unlikely that marketing of the treatment would cover the costs of development), and
- there is no satisfactory currently available treatment or if such a treatment option exists, the new treatment should offer significant benefit to those affected by the condition.

Considering the above criterion, treatments for MND would be strong candidates for orphan status in Europe. There is a debate in healthcare decision making over whether special consideration should be given to the funding and provision of treatments for rarer diseases. Several studies have shown that people appear to not have a preference to fund rarer diseases over more common ones [101,102]. Some of these studies, however, have also shown that some factors may incline people to divert more funding to rare diseases. These factors include the severity of the disease and whether there are any alternative treatments currently available to treat it [103]. Indeed, NICE highlighted these considerations when assessing riluzole [95]. Decisions to fund expensive treatments for rare diseases means that there is less funding for other conditions. NICE, informed by a report from its citizens council, does not regard disease rarity in itself to be a justification to recommend use of expensive drugs, but rarity does often play an indirect role in both its highly specialised technology program [94] and its end of life criteria [96] (both which allow a higher willingness-to-pay cost per QALY threshold). So, while orphan status is granted to treatments for rare diseases, NICE does not necessarily give formal special considerations to orphan status treatments in its HTA

programme. Treatments for very rare conditions (which will also be classed as orphan drugs), which meet NICE's Highly Specialised Technology criterion, NICE uses a higher acceptable ICER threshold (£100,000 per QALY gained) and allows treatments which provide substantial QALY gains to have ICERs up to £300,000 per QALY gained. Treatments which go through NICE's HST programme are more likely be allowed to be assessed using a 1.5% discount rate (due to the nature of conditions considered in the HST programme), as opposed to the standard 3.5% rate, which results in more favourable cost-effectiveness results (as future health benefits value is increased). NICE outlines the creation applied in deciding which treatments are considered under its HST methods [94], which outlines that:

- The target patient group for the technology in its licensed indication is so small that treatment will usually be concentrated in very few centres in the NHS;
- The target patient group is distinct for clinical reasons;
- The condition is chronic and severely disabling;
- The technology is expected to be used exclusively in the context of a highly specialised service;
- The technology is likely to have a very high acquisition cost;
- The technology has the potential for life long use;
- The need for national commissioning of the technology is significant.

MND can be considered a rare disease although, due to the short life expectancy associated with the condition, the lifetime risk of having MND is around 1 in 300 to 350 [104,105]. As highlighted, this level of rarity also means that treatments for MND can be considers as orphan drugs, which allows manufacturers to gain certain benefits which help reduce the costs of bringing the treatment to market and increase the commercial opportunities if marketing authorisation is granted. MND is also certainly a severe condition with limited treatment options. While this thesis does not directly address the issue of funding for rare diseases, it is important to note that (due to its poor prognosis) MND can be thought of as a rare disease and this may impact on funding and drug development considerations. A strong motivation for this thesis comes the desire to address the fact that the evidence base in terms of health economics is limited for MND, due to its rarity. Many aspects of the thesis are tied

together by the issues of rarity and generating relevant evidence for HTA of potential new treatments (see section 1.7).

Development of drugs by pharmaceutical companies can be less lucrative, due to the smaller populations of patients with these conditions. However there has been criticism for some policy initiatives that incentivise drug manufacturers to develop treatments for rare conditions, as for some companies the revenue gained from the sale of orphan drugs make up a large proportion of their profits [106]. Incentives offered in the EU include longer patent durations and tax breaks and some commentators have questioned if these incentives are too generous [107]. Many manufacturers of drugs for treating rare diseases charge high prices, which leads to access issues for patients as these treatments struggle to be deemed cost-effective.

1.7 Aims and objectives of this thesis

The overall aim of the thesis is to identify and describe the health economic evidence base in MND and add to this with relevant information on which can inform future health economic assessments of MND treatments. It also aims to provide insights into the cost burden of MND on the NHS and further inform on the impact of the condition on patients. A key consideration in the analysis undertaken in this thesis was to present the results of the empirical data by the structures of well accepted MND staging systems, making them relevant to current needs.

The aims and objectives outlined in this section cover fundamental aspects required to inform health decision-making for new MND treatments, therefore the scope of research is aligned to the NICE reference case (such as systematic review, outcomes, measuring and valuing health, costs from an NHS perspective, cost-utility analyses– see table 1.1). Discussion on some topics which may expand this scope is also presented. These objectives contributed to the overall aim of the thesis.

Aims and objectives of chapters in thesis

Chapter two aims to provide a summary and a methodological critique of the current evidence base in terms of research in health economic aspects of MND. The objectives by which addresses this aim involves a systematic review, which assesses the current evidence

regarding cost, health utility and economic evaluations in MND. This assessment also outlines both the results reported in the various included studies but also, perhaps more importantly, provides a critic of the methodology used across these analyses. A comprehensive review allows important gaps in the literature to be identified and recommendations to be made on how the rest of the research in this thesis can help to address some of these uncertainties. This is an important first piece of research as no systematic review has previously combined the range of studies which may inform healthcare provision decision-making or provided a narrative on the methods used.

Chapter three aims to investigate if there is a statistical link between the ALSFRS-R, the most commonly used measure in MND clinical trials, and the Euro-QoL EQ-5D-5L measure, a commonly used generic preference-based measure. The chapter's objectives are to provide analysis which makes use of the earlier described TONiC dataset which included outcomes for both of these measures from a UK MND population. This linking, known as mapping or cross walking, adds value when the EQ-5D has not been collected within a clinical trial for MND, which is frequently the case. This analysis also makes use of the multi-level aspect of the ALSFRS-R measure, testing the statistical merits of using the index, domain and individual item scores to estimate EQ-5D-5L utilities. The chapter also reports results of this mapping analysis when using the ALS utility index, a preference-based disease specific measure for MND which is structured using certain ALSFRS-R items.

Chapter four's aim is to estimate healthcare resource use costs, from the NHS perspective, and health utilities associated with MND and its progression from a UK MND population using relevant MND staging systems. The chapter reports some key cost drivers and characteristics which influence health utility values. The objectives for this chapter includes the use of two well accepted clinical staging systems (Kings and MiToS) to provide information on these two essential health economic parameters, presented in terms of the clinical stages of both systems. The objectives allow two different and complementary staging systems to be used to show how different ways of framing the natural progression of MND can affect costs of healthcare provision and the impact on health-related quality of life. The evidence generated from chapter four will add to the evidence base in both costs and health utilities and provide data generalisable to the UK MND population as the data also comes from the TONiC database. This data may also be used to assess new treatments for MND.

One such potential treatment is edaravone and the data presented in chapter four is used as the basis for a health economic evaluation of edaravone for the treatment of MND in chapter five. Chapter five's aim is to estimate the cost-effectiveness of edaravone from a UK health payer (NHS) perspective. The objectives of the chapter is to use Markov modelling, a well-accepted method in chronic diseases, to extrapolate beyond the clinical trial data. This evaluation also makes use of data from the pivotal edaravone trial and the previously described large PRO-ACT dataset, which allowed matching of patients to the strict clinical trial inclusion criteria. Whilst edaravone is approved in for marketing in the U.S and Japan, the manufacturer has currently withdrawn its application to the EMA. The reasons for this have been explained earlier in this chapter. A further objective was to provide insights on potentially important considerations for other potential treatments for MND. Chapter five presents a range of sensitivity and scenario analysis to give an indication to how much uncertainty surrounds the ICER estimate and thoughts on the challenges that other potential treatments (such as those described in section 1.3) may face, which may be different to those faced by edaravone.

This thesis will provide useful information, which is compatible with accepted MND clinical staging systems, to critically assess new treatments for MND. This new information will address the need for robust important parameter inputs to inform decision making. The motivation for this thesis comes from the current limited literature in health economic analyses concerning MND and the real possibility of future treatments becoming available. The principal findings of this body of work are outlined in the discussion chapter along with the strengths and weaknesses of the analyses undertaken. The discussion chapter also puts forward recommendations for future research in health economics regarding MND.

1.8 Author contribution

Outlined in this section are the contributions to the work in each chapter by myself (Alan Moore, AM) and my supervisory team (Professor Dyfrig A. Hughes; DAH and Professor Carolyn A. Young: CAY)

Chapter 1: Initial draft by AM. DAH and CAY provided conceptual advice and critical comments.

Chapter 2: Search strategy, systematic literature search, data extraction and initial draft by AM. DAH and CAY provided a second review of the extracted data, provided conceptual advice and critical advice.

Chapter 3: Data analysis and initial draft by AM. DAH and CAY provided conceptual advice and critical comments. TONiC data released by CAY.

Chapter 4: Data analysis and initial draft by AM. DAH and CAY provided conceptual advice and critical comments. TONiC data released by CAY.

Chapter 5: Data analysis and initial draft by AM. DAH and CAY provided conceptual advice and critical comments.

Chapter 6: Initial draft by AM. DAH and CAY provided conceptual advice and critical comments.

Preface to Chapter two

As has been discussed, MND is a condition which greatly impacts on health-related quality of life and is associated with significantly reduced life expectancy. There are limited current treatment options, however there are several treatments which may prove effective in ongoing clinical trials. Health economics is an important part of healthcare provision, and new treatments will need to demonstrate value for money and cost-effectiveness.

To be able to estimate the cost-effectiveness of new MND treatments, we need a robust health economic framework and appropriate input parameters. Chapter two looks at the current evidence base and reports the results of a systematic review which aimed to include health economic evaluations, cost and utility studies to in MND. It's focus is on the methods used in these studies and the appropriateness of those methods used.

Chapter two

Economic Studies in Motor Neurone Disease: A Systematic Methodological Review

Abstract

BACKGROUND: Motor Neurone Disease MND) is a devastating condition which greatly affects patients' quality of life and limits life expectancy. Health technology appraisals of future interventions in MND need robust data on costs and utilities. Existing economic evaluations have been noted to be limited and fraught with challenges.

OBJECTIVE: The aim was to identify and critique methodological aspects of all published economic evaluations, cost studies and utility studies in MND.

METHODS: We systematically reviewed all relevant published studies in English from 1946 until January 2016, searching the databases of Medline, EMBASE, Econlit, NHS Economic Evaluation Database (NHS EED) and the Health Economics Evaluation Database (HEED). Key data were extracted and synthesised narratively.

RESULTS: A total of 1,830 articles were identified, of which 15 economic evaluations, 23 cost and 3 utility studies were included. Most economic studies focused on riluzole (n=9). Six studies modelled the progressive decline in motor function using a Markov design but did not include mutually exclusive health states. Cost estimates for a number of evaluations were based on expert opinion and were hampered by high variability and location-specific characteristics. Few cost studies reported disease stage specific costs (n=3) or fully captured indirect costs. Utilities in 3 studies of MND patients used the EQ-5D questionnaire or standard gamble, but included potentially unrepresentative cohorts and did not consider any health impacts on caregivers.

CONCLUSION: Economic evaluations in MND suffer from significant methodological issues such as a lack of data, uncertainty with the disease course and use of inappropriate modelling framework. Limitations may be addressed through the collection of detailed and representative data from large cohorts of patients.

2.1 **Introduction**

Motor Neurone Disease or Amyotrophic Lateral Sclerosis (hereafter referred to as MND) is a progressively degenerative condition. The disease affects the motor neurones in the brain and spinal cord which severely impacts patients' basic functioning such as walking, communication and breathing, and can additionally adversely affect cognitive abilities [108]. These impair patients' health-related quality of life significantly [109]. Currently treatment for MND is focused on palliative care with the aim of sustaining a high quality of life for as long as possible. Estimated survival time from diagnosis is between 3 and 5 years [19]. Due to the extent of the disability, patients with MND have dependency on carers to help with their daily needs. This need is usually met by partners or family members of the patient and, due to the nature of care required, places a significant physical and emotional burden on their lives [110].

MND is a rare disease with incidence and prevalence rates varying by country and region. A recent systematic review of its epidemiology reported European, North American and Asian incidence rates of 2.08, 1.8 and 0.46 per 100,000 population per year, respectively [111]. Prevalence rates were reported as 5.4, 3.4 and 2.01 per 100,000 population in these regions. In the United Kingdom there are an estimated 4,000 people living with MND [48].

The economic costs of MND are high, both in terms of direct medical costs to health providers, non-medical costs incurred by patients and their caregivers, and indirect costs through loss of employment. Costs vary over the trajectory of the condition, and are dependent on disease manifestation, progression, and duration of survival [112]. To date, however, there has been a limited number of economic evaluations of interventions for MND, with the majority focused on riluzole which is the only disease-modifying drug currently approved. With the prospect of new treatments for MND [63], there will be an increased need for robust economic data and modelling framework for assessing their cost-effectiveness. The aim of this article is to systematically review sources of costs and utilities, and provide a critique of the data and methods used in economic studies of MND.

2.2 Methods

This review was conducted according to the Centre for Reviews and Dissemination's (CRD) guidance for undertaking reviews in health care [113], and reported with alignment to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guideline, where applicable [114].

2.2.1 Search Strategy

Systematic searches were undertaken to identify economic evaluations, studies detailing costs and studies which estimated health state utilities in patients with MND. The search terms are listed in Appendix 3. The databases searched (from 1946 to January 2016) were: Medline, EMBASE, Econlit, NHS Economic Evaluation Database (NHS EED), and the Health Economics Evaluation Database (HEED). The references of included papers were checked for any further articles for inclusion.

2.2.2 Inclusion criteria and study selection

The review included studies reporting economic evaluations, detailed costs and health utilities relating to MND. Studies not published in English were excluded from the review. Titles were screened independently by two reviewers. Articles deemed by either reviewer to meet the inclusion criteria were screened independently on abstract with any disagreements resolved by a third independent reviewer. The full texts were retrieved and assessed according to the inclusion criteria.

2.2.3 Data extraction

Data forms were created for the economic evaluations and cost studies included in the review and key details relating to the methods of included studies extracted and tabulated (Tables 1 and 2). Cost and utility value data from these studies were also recorded along with the corresponding 2014/15 value of costs in pounds sterling (GBP) (Table 3). Currency conversions were undertaken using data from the International Monetary Fund (IMF) [115] and costs were inflated using the Hospital and Community Health Services (HCHS) pay and prices index [116].

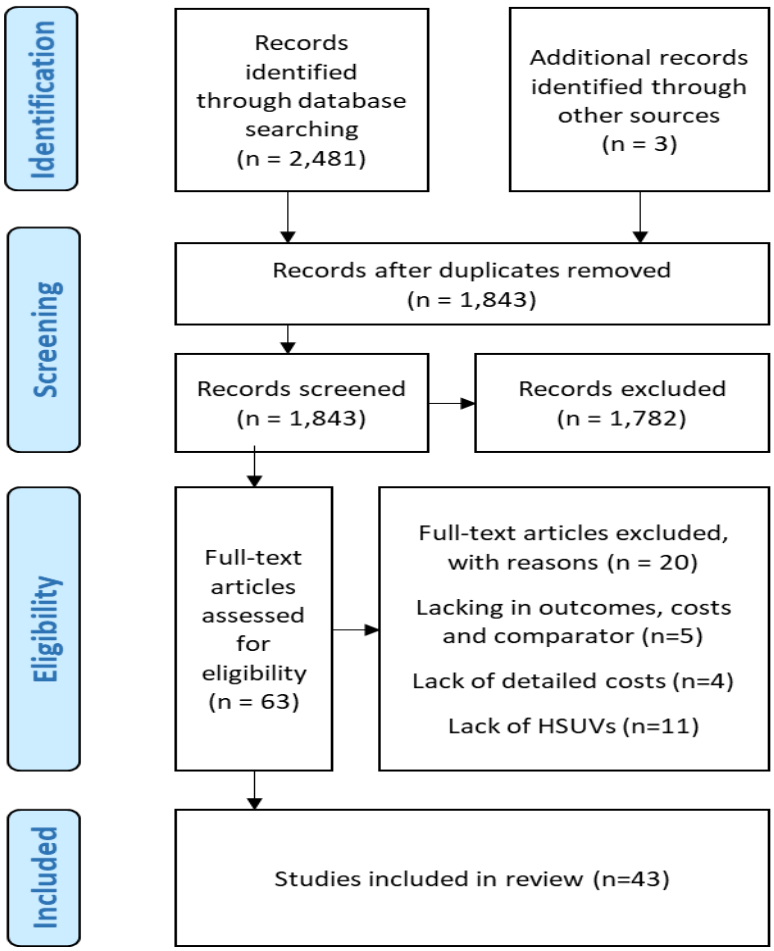
2.2.4 Analysis of results

Important methodological features were summarised, and critiqued within a narrative review.

2.3 Results

A total of 1,830 articles were identified, of which 60 were considered potentially relevant and 41 eligible for inclusion in the review. The PRIMSA flow diagram shows the number of included studies at the various stages of the review process (Figure 2.1).

Figure 2.1 – PRIMSA flow diagram



2.3.1 Study characteristics

The systematic review identified 13 economic evaluations, 2 updates of economic evaluations, 23 cost studies, and 3 studies reporting health utilities (Tables 1, 2 and 3).

The majority of economic evaluations were conducted in the UK [120-124,128,130,131] (n=8) followed by North America [117,119,126,127] (n=4), Italy [118,125] (n=2) and Israel [129], showing the high concentration of studies originating in a few countries. Eight studies reported a cost utility analysis [119-124,126,127], 6 studies performed cost effectiveness analysis [13,14,21,24,26,27], and 1 study carried out a cost-benefit analysis [129]. Eleven evaluations adopted a third party payer perspective, such as national health services [117,118,120-125,128,130,131], 1 study adopted a societal viewpoint [129], while 3 studies presented results from both perspectives [119,126,127]. More recent economic evaluations tended to report only direct medical costs to health service providers.

Studies focusing solely on costs were predominantly North American [132,134,137,138,141,144,147,148,150,152-154] (n=12) or European

[135,136,140,142,143,145,146,149,151] (n=9) with two from Asia [133,139]. Cost studies adopted a health services perspective [132,135,139,143,147,148,150-152] (n=9), societal perspective [137,144,145,149,153] (n=5) or both [133,134,136,138,140-142,146,154] (n=9). Studies reported costs for a variety of categories, including: treatments [134,136-138,140,141,145,146,148,149,151,152] (n=12), places or methods of delivering care [132,133,135,139,142,143,147,150] (n=8), home ventilation [153,154] (n=2) and mobility devices [40]. However, only 3 studies reported disease stage specific costs [133,146,151].

Studies of health state utility reported disease stage utilities by five (mild, moderate, severe, terminal and death) [155,156], or two (mild and severe) [146] health states. All studies elicited utilities from patients with MND, based on structured interviews with MND patients [155,156], or from a postal questionnaire [146]. These used a combination of the EQ-5D-3L, visual analogue scale (VAS) and standard gamble to measure utility.

Table 2.1 - Methods of economic evaluations in MND

Author(s), Year, Country	Definition of MND, Source population, Number of patients	Intervention and comparator	Economic evaluation	Cost perspective	Clinical data	Measurement of benefits	Methods of estimating survival	Measurement of costs	Sensitivity analysis
Alanazy et al 2014 [117] Canada	Not stated Clinic population 333 patients	Immunoglobulin/ standard care	Cost effectiveness analysis	Health service	Observational data	Diagnosis rate	None	Resource use from institutional data. Local cost tariffs used	None
Vitacca et al 2010 [118] Italy	El Escorial criteria Clinic population 39 patients	Telephone assisted consultation/ home visits by health staff	Cost effectiveness analysis	Health service	Observational data	Number of avoided hospitalizations	None	On call telephone access, home visits, equipment, rehabilitation costs and resource use from institutional data. Local cost tariffs used.	None
Gruis et al 2005 [119] United States	Not stated Hypothetical cohort Not stated	Non-invasive ventilation/ standard care	Cost utility analysis Markov model with 5 health states: based on functioning of three regions (speech, arms and legs) derived from Rivere et al [157]	Health service and societal	Hypothetical data	QALYs derived form a patient population (n=77) by standard gamble approach [155]	None	Costs of non-invasive ventilation and accessories for patients tolerant to treatment. One month rental and accessories costs for those intolerant to treatment. Unit costs taken from Medicare fee schedule. Resource use is estimated on the uptake levels of the treatment.	One way
Aventis Pharma	Clinical diagnosis of	Riluzole/ Standard care	Cost utility analysis	Health service	Randomised controlled	QALYs derived from a patient	Linear interpolation	Resource use taken from consultation	Two way

2000 [122] and updates /revisions [120,121] United Kingdom	definite or probable MND Clinical trial population 954 patients		Markov model with 5 health states: based on functioning of three regions (speech, arms and legs) derived from Rivere et al [157]		trial [158]	population (n=77) by standard gamble approach [155]		with experts. Cost data taken from Munsat et al using local tariffs [151]	
Bryan et al 2000 [123] United Kingdom	Clinical diagnosis of definite or probable MND Clinical trial population 959 patients	Riluzole/ Standard care	Cost utility analysis Markov model with 5 health states: based on functioning of three regions (speech, arms and legs) derived from Rivere et al [157]	Health service	Randomised controlled trial [158]	QALYs derived from a patient population (n=77) by standard gamble approach [155]	Weibull and Gompertz models	Riluzole and monitoring costs taken from the published literature and resource use taken from RCT [158]	Scenario analysis
Stewart et al 2000 [124] United Kingdom	Clinical diagnosis of definite or probable MND Clinical trial population 959 Patients	Riluzole/ Standard care	Cost utility analysis Markov model with 5 health states: based on functioning of three regions (speech, arms and legs) derived from Rivere et al [157]	Health service	Randomised controlled trial [158]	QALYs derived from a patient population (n=77) by standard gamble approach [155]	Weibull model	Riluzole and monitoring costs taken from the British National Formulary. Resource use is taken from RCT [158]	One way
Messori et al 1999	Clinical diagnosis of	Riluzole/ Standard care	Cost effectiveness	Health services	Randomised controlled	Survival	Gompertz model	Riluzole and monitoring costs	One way and scenario

[125] Italy	definite or probable MND Clinical trial population 633 patients		analysis		trials [158,159]			taken from the published literature. Resource use taken from RCT data [158,159]	analysis
Ackerman et al 1999 [126] United States	Clinical diagnosis of sporadic MND Clinical trial population 177 patients	Recombinant Human Insulin-Like Growth Factor 1 Therapy/ Standard care	Cost utility analysis Markov model with 5 health states based on lung function defined by forced vital capacity score (FVC)	Health service and societal	Randomised controlled trial [161]	QALYs derived from a panel of experts (n=10) using the standard gamble approach	Exponential distribution	In- and out-patient procedures, home health, hospice care costs and resource use measured from RCT [161]	One way
Ringel et al 1999 [127] United States	Clinical diagnosis of definite or probable MND Clinical trial population 1135 patients	Hypothetical therapies/ Standard care	Cost utility analysis Markov model with 5 health states based on lung function defined by forced vital capacity score (FVC)	Health service and societal	Randomized controlled trail [161]	QALYs derived from hypothetical utility scores	None	Resource use derived from RCT [159] Direct costs and costs related to reduced productivity included, also taken from RCT using national tariffs [161]	Probabilistic sensitivity analysis
Gray 1998 [128] United Kingdom	Clinical diagnosis of definite or probable MND Clinical trial population 959 patients	Riluzole/ Standard Care	Cost effectiveness analysis	Health services	Randomised controlled trial [158]	QALYs derived from hypothetical utility scores	None	Monthly riluzole and tracheostomy costs taken from British National Formulary. Resource use taken from RCT [158]	One way
Ginsberg and Lev 1997 [129] Israel	Not stated Hypothetical cohort Not stated	Riluzole/ Standard care	Cost benefit analysis	Health services and societal	Randomised controlled trial [158]	Survival	None	Direct costs to health service and Indirect productivity costs.	One way

								Unit costs obtained thorough government publications. Resource use is based on estimated usage	
Chilcott et al 1997 [130] United Kingdom	Clinical diagnosis of definite or probable MND Clinical trial population 959 patients	Riluzole/ Standard care	Cost effectiveness analysis	Health services	Randomised controlled trial [158]	Survival	Kaplan-Meier estimator	Riluzole and monitoring costs obtained through national tariffs. Resource use based on length of treatment time (months) per patient	Scenario analysis
Booth-Clibborn et al 1997 [131] United Kingdom	Clinical diagnosis of definite or probable MND Clinical trial population 959 patients	Riluzole/ Standard care	Cost effectiveness analysis	Health services	Randomised controlled trails [158,159]	Survival	None	Riluzole and monitoring costs taken from British National Formulary. Resource use based on RCTs [158,159]	None

Table 2.2 - Methods of cost studies in MND

Author(s), Year, Country	**Definition of MND, Source population, Number of patients**	**Treatment**	**Cost perspective**	**Source of resource use data**	**Items of resource use**	**Unit costs**
Boylan et al 2016 [132] United States	El Escorial criteria Clinic population 1117 patients	Multi-disciplinary centre care	Health services	Institutional data	Staff time Medical supplies Medical equipment Overhead costs	Local tariffs
Oh et al 2015 [133] South Korea	El Escorial criteria Clinic population 151 patients	Standard care	Health services and societal	Interviews with patients and institutional data	Loss of income Hospital care	National tariffs
Obermann and Lyon 2015 [134] United States	Not stated Home based population 1 patient	Various treatments	Health services and societal	Longitudinal survey completed by family members	Hospital care Home care Equipment Home renovations Transport Home care	Local tariffs
Connolly et al 2015 [135] Ireland	Not stated Clinic population 250 patients	Multi-disciplinary centre and social care	Health services	Institutional data and Interviews with patients	Specialist Care Social Care	Local tariffs
Attanasalais et al 2015 [136] Greece	Not stated Clinic population 33 patients	Various treatments	Health services and societal	Institutional data and interviews with patients and caregivers	Loss of income	National tariffs
Gladman et al 2014 [137] Canada	El Escorial criteria Home based population 50 patients	"Out of pocket" procedures	Societal	Interviews with patients and caregivers	Medical Mobility Home renovations Loss of income	Local tariffs
Larkindale et al 2013 [138] United States	Not stated Clinic population 600 patients	Various treatments	Health services and societal	Insurance databases and patient surveys	Medical Loss of income	National tariffs
Kang et al 2013 [139] Taiwan	Not stated Clinic population 30 patients	Hospice care	Health services	Institutional data and health insurance claims	General hospice care	Local tariffs
Jennum et al 2013 [140] Denmark	Clinical diagnosis of MND Clinic population 2,384 patients	Various treatments	Health services and societal	National health and social statistics databases	Medical costs Welfare costs	National tariffs
Muscular Dystrophy Association 2012 [141] United States	Clinical diagnosis of MND Clinic population 954 patients	Various treatments	Health services and societal	Family and caregiver surveys	Medical costs Loss of income	National tariffs
De Alemeida 2012 [142] Portugal	Not stated Clinic and home based populations	Home tele-monitoring care	Health services and societal	Institutional data	Hospitalisation Outpatient Transport Equipment	National tariffs

	39 patients				Loss of income	
Vitacca et al 2012 [143] Italy	El Escorial criteria Clinic population 73 patients	Home tele-monitoring care	Health services	Institutional data	Staff time	National tariffs
Ward et al 2010 [144] United States	Not stated Clinic population 45 patients	Power wheelchairs	Societal	Patient surveys	Wheelchair	Local tariffs
Schepelmann et al 2010 [145] Germany	El Escorial criteria Clinic population 107 patients	Various treatments	Societal	Patient survey and institutional records. Human capital approach used for indirect costs	All disease related expenditure	Local Tariffs
Lopez-Bastida et al 2009 [146] Spain	Not stated Clinic population 63 patients	Various treatments	Health services and societal	Patient survey	Hospital stay Medicines Transport Loss of income	National tariff and local tariffs
Elman et al 2006 [147] United States	Clinical diagnosis of MND Clinic population 25 patients	Hospice care	Health services	Institutional data	Length of stay Staff Transport Medicines	Local tariffs
Forshew and Bromberg 2003 [148] United States	Not stated Clinic population	Various treatments	Health services	Doctor survey	Drug costs	National tariffs
Wasner et al 2001 [149] Germany	Clinical diagnosis of MND Home based population 92 patients	Alternative medicines	Societal	Patient survey	Acupuncture Homeopathy Naturopathy Esoteric	Local tariffs
Lechtzin et al 2001 [150] United States	El Escorial criteria Clinic population 1600 patients	Hospital care	Health services	Nationwide in-patient sample database	Length of stay costs	National tariffs
Munsat et al 1998 [151] United Kingdom	Not stated Clinic population	Standard care	Health services	Consultation with neurologists	Hospitalization Physician time Outpatient care Palliative drug cost Medical devices	Local Tariffs
Klein and Forshew 1996 [152] United States	Not stated Clinic population	Various treatments	Health services	Consultation with neurologists	Diagnosis costs Palliative costs Life support	National Tariffs
Sevick et al 1996 [153] United States	Not stated Clinic population 277 patients	Home based ventilator care	Societal	Patient and caregiver survey	Home help Occupational therapy Physical therapy Transport Ventilation care	Local Tariffs
Moss et al 1996 [154] United States	Not stated Clinic population 50 patients	Hospital and home based ventilator care	Health services and societal	Patient and caregiver survey	Hospital care Equipment Out of pocket expenses	National and Local Tariffs

2.3.2 Modelling methodology

Eight studies, including the more recent evaluations, used Markov architecture which allow for progressive decline in motor function to be modelled [119-124,126,127]. The models attach costs and utilities to health states and allow patient cohorts to pass through states until they reach the (absorbing) death state or a pre-determined severely low functioning level. Health states within these models were defined by adaptation of Rivere et al. [157] who first modelled MND using the Markov model [119-124], Appel ALS scores [126] or according to forced vital capacity scores (FVC) [127]. Transition probabilities of subjects through the various health states were calculated using data from randomised control trials of riluzole [119-124], recombinant human insulin-like growth factor-1 (rhlGF-1) [126], and brain-derived neurotrophic factor (BDNF) [127].

Models used various techniques to estimate survival beyond the data available from randomised controlled trials (RCTs). Three studies used a linear function [120-122], and one an exponential function [126] to extrapolate trial data. Although these were deemed to have fit the data well by study authors, they are not the correct functional form for survival analysis. The constant hazard rate model, which gives the exponential distribution, assumes the property of no-aging [162]. One study used a Weibull model [124] (based on a power hazard rate model). One study used a Gompertz model (exponential hazard rate model), without presenting goodness of fit [125], and one study used both a Weibull and a Gompertz model [123] to explore differences in model fit.

2.3.3 Resource use and costs

Twenty-two studies reported direct costs only [117,118,120-125,128,130-132,135,139,143,144,147-151], while 16 reported both direct and indirect costs [119,126,127,129,133,134,136-138,140-142,145,146,153,154].

Studies which included direct costs estimated resource use from medical records [117-119,132,135,136,141-143,147] (n=10), RCTs [123-131] (n=9), surveys [134,141,144,146,149,153,154] (n=7), utilization patterns based on consultation with neurologists with MND expertise [120-122,151,152] (n=5), national databases [140,150] (n=2), structured interviews with patients [137,145] (n=2), insurance claim data [138] and a mixture of medical records and insurance claim data [139]. Indirect costs were obtained via patient surveys [119,127,134,136,138,141,142,146,153,154] (n=10) and interviews [126,133,137,145] (n=4), and national databases [129,140] (n=2).

Unit costs came from institutional records [117,118,132,133,135-137,139,142,143,147,149,150] (n=13), national databases [119,125,128-131,140,141,146,148] (n=10), the published literature

[120-124,127] (n=6), surveys [134,144,145,153,154] (n=5), consultation with MND experts [151,152] (n=2), insurance claim data [138] and estimation of drug costs from the manufacturer [126].

Some studies defined standard care costs [120,123,124,126,129,131] (n=6), but descriptions varied by location and setting.

Indirect unit costs were gathered by surveys [126,127,133,134,137,138,142,145,153,154] (n=10), national databases [119,140,141,146] (n=4) and using the national minimum [136] and average wage [129].

Key cost data used in economic evaluations in MND are presented in Table 3. Many of the cost inputs originate from the same sources, suggesting a limited evidence base [120-124]. Furthermore, costs varied by location, with the annual price of riluzole, for example, reported as £6,429 in the United Kingdom and £9,487 in the United states (2014/15 adjusted values in £GBP). Table 4 presents the main data from cost studies in MND. Costs and cost categories include length of hospital stays [139,147,150], ventilation [134,153,154], complementary medicines [149] and mobility [144]. Differences in costs within countries may be attributed to type of treatments considered, methods of data collection or source populations [134,141,147]. The diverse cost estimates and categories highlights the challenges of generalising results, with the need for more detailed and encompassing cost of illness studies.

Tables 2.3 - Key cost and utility data in economic evaluations in MND

Author(s), Year of Publication, (cost data year)	**Mean direct cost per patient (2015 cost in £)**	**Health state utilities**
Alanazy, White and Korngut 2014 (2013) [117] Canada	Investigative testing: Can$ 10,686 (£5,861) (lifetime cost) Control: Standard care costs assumed equal in both groups	None
Vitacca et al 2010 (2005) [118] Italy	Tele assisted care: €425 (£369) per month Standard care: €239 (£214) per month	None
Gruis, Chernew and Brown 2005 (2003) [119] United States	Non-invasive ventilation: $3,132 (£2,584) per annum Trial of non-invasive ventilation in patients who prove to be intolerant: $467 (£385) (lifetime cost) Control (Standard care): Standard care costs assumed in both groups	Mild State: 0.8 Moderate State: 0.6 Severe State: 0.5 Terminal State: 0.4

Aventis Pharma 2000 (1998) [122] and updates / revisions [120,121] United Kingdom	Intervention (riluzole): £3,742 (£6,429) per annum + Standard care costs Control Group (Standard care annual costs): Mild State Care: £1,224 (£2,068) Moderate State Care: £805 (£1,360) Severe State Care: £1,754 (£2,963) Terminal State Care: £3,231 (£5,458)	Mild State: 0.79 Moderate State: 0.67 Severe State: 0.71 Terminal State: 0.45
Bryan, Barton and Burls 2000 (1999) [123] United Kingdom *Updated analysis of Stewart et al [124]	Intervention (riluzole): £3,930 (£6,385) per annum + Standard care costs Control (Standard care annual costs): Mild state care: £1,237 (£2,056) Moderate state care: £834 (£1,352) Severe state care: £1,771 (£2,957) Terminal state care: £3,263 (£5,444)	Mild State: 0.79 Moderate State: 0.67 Severe State: 0.71 Terminal State: 0.45
Stewart et al 2000 (1999) [124] United Kingdom	Intervention (riluzole): £10.21 (£16.59) per day; monitoring: £17 (£28) per month Control (Standard care annual costs): Mild state care: £1,237 (£2,056) Moderate state care: £834 (£1,352) Severe state care: £1,771 (£2,957) Terminal state care: £3,263 (£5,444)	Mild State: 0.79 Moderate State: 0.67 Severe State: 0.71 Terminal State: 0.45
Messori et al 1999 (1996) [125] Italy	Intervention (riluzole): US$8,736 (£9,487) per annum Control: standard care costs assumed to be equal in both groups	None
Ackerman et al 1999 (1996) [126] United States	rhlGF-1 therapy: US$46,860 (£51,295) (lifetime cost) Control (Standard care): $7,754 (£8,494) (lifetime cost)	Appel ALS score 40 - 59: 0.89 Appel ALS score 60 - 86: 0.82 Appel ALS score 87- 109: 0.41 Appel ALS score 110 - 128: 0.01 Appel ALS score 129 - 164: -0.53
Ringel, Woolley and Wilkins 1999 (1996) [127] United States	Direct and Indirect costs of MND (per month): Forced Vital Capacity 90+: US$1,395 (£1,571): Forced Vital Capacity 60-90: US$1,770 (£1,994): Forced Vital Capacity 30-60: US$3,046 (£3,441) Forced Vital Capacity 0-30: US$4,746 (£5,345)	Forced Vital Capacity 90+: 0.9 Forced Vital Capacity 60-90: 0.8 Forced Vital Capacity 30-60: 0.6 Forced Vital Capacity 0-30: 0.4 (hypothetical values)
Gray 1998 (1997) [128] United Kingdom	Intervention (riluzole): Non-tracheostomy patients: £286 (£491) per month; patients post-tracheostomy: £300 (£504) per month Control (Standard care): standard care costs assumed equal in both groups	Various scenarios: survival time with utilities of 1, 0.8 and 0.5 (hypothetical values)
Ginsberg and Lev 1997 (1996) [129] Isreal	Intervention (riluzole): $3,004 (£3,288) (lifetime costs)	None
Chilcott et al 1997 (1996) [130] United Kingdom	Intervention (riluzole): £3,720 (£6,568) per annum Control (Standard care): Standard care costs assumed to be equal in both groups	None

Booth-Clibborn et al 1997 (1996) [131] United Kingdom	Intervention (riluzole): £15,000 (£25,771) (lifetime costs) Control (Standard care): Standard care costs assumed to be equal in both groups	None

Table 2.4 - Principal direct and indirect cost data in cost studies in MND

Author(s), Year of Publication, (cost data year)	**Mean direct cost per patient (2015 cost in £)**	**Mean indirect cost per patient (2015 cost in £)**
Boylan et al 2016 (2007) [132] United States	Clinic costs: $507 (£497) per clinic visit	Not considered
Oh et al 2015 (2013) [133] South Korea	Healthcare costs (per month): Stage 1: Not stated Stage 2: $3,181 (£2,027) Stage 3: $2,773 (£1,767) Stage 4: $4,415 (£2,722)	Patient lost wages (per month): Stage 1: Not stated Stage 2: $1,155 (£736) Stage 3: $1,889 (£1,204) Stage 4: $2,629 (£1,675)
Obermann and Lyon 2015 (2005) [134] United States	Ventilation: $212,430 (£157,372) (lifetime cost) Hospital Care: $114,558 (£84,866) (lifetime cost)	Caregiver costs: €669,150 (£495,719) (lifetime cost)
Connolly et al 2015 (2010) [135] Ireland	Health and social care costs: €1,795 (£1,255) per month	Not considered
Attanasalais et al 2015 (2013) [136] Greece	Direct medical costs: €4,305 (£2,830) per annum	Informal care and productivity losses: €3,145 (£2,168) per annum
Gladman et al 2014 (2012) [137] Canada	Healthcare provider and "out of pocket costs": Can$32,337 (£21,455) per annum	Lost wages of patients and caregivers: Can$56,821 (£37,700) per annum
Larkindale et al 2013 (2010) [138] United States	Total direct and indirect costs per patient: $63,693 (£48,468) per annum (cost not disaggregated)	
King et al 2013 (2007) [139] Taiwan	Hospice care: NT$ 47,180 (£2,962) (lifetime cost)	Not considered
Jennum et al 2013 (2009) [140] Denmark	Medical costs: €18,918 (£16,514) per annum	Spouse earnings: Increased €3,420 (£2,985) per annum
Muscular Dystrophy Association 2012 (2010) [141] United States	Medical costs: $30,934 (£23,165) per annum	Not considered
De Alemedia 2012 (2010) [142] Spain	Tele monitoring care: €8,909 (£9,030) per annum Standard care: €19,952 (£19,952) per annum	Not stated
Vitacca et al 2012 (2007) [143] Italy	Tele assistance: €105 (£84) per month	Not considered
Ward et al 2010 (2008) [144] United States	Wheelchair costs: $26,404 (£20,481) (lifetime cost)	Not considered

Schepelmann et al 2010 (2009) [145] Germany	Medical costs: €14,980 (£13,076) per annum	Patient lost earnings: €21,400 (£18,680) per annum
Lopez-Bastida et al 2009 (2004) [146] Spain	Medical costs (lifetime costs): High severity patients: €34,729 (£31,182) Low severity patients: €6,735 (£6,034)	High severity patients: €8,000 (£7,168) Low severity patients: €10,265 (£9,198)
Elman et al 2006 (2003) [147] United States	Hospital stay costs: $5,623 (£5,416) (lifetime cost)	Not considered
Forshew and Bromberg 2003 (2002) [148] United States	Various drug costs	Not considered
Wasner et al 2001 (2000) [149] Germany	Alternative medicines: €4,142 (£4,293) (lifetime cost)	Not considered
Lechtzin et al 2001 (1996) [150] United States	Hospital stay costs: $19,810 (£21,685) (lifetime cost)	Not considered
Munsat et al 1998 (1996) [151] United Kingdom	Standard care costs (per annum) Mild State Care: £1,185 (£2,072) Moderate State Care: £800 (£1,370) Severe State Care: £1,698 (£2,989) Terminal State Care: £3,128 (£5,498)	Not considered
Klein and Forshew 1996 (1995) [152] United States	Diagnosis costs: $10,000 - $ 20,000 (£10,946 - £21,893) (lifetime cost) Mechanical Ventilation: $199,500 (£218,382) per annum	Not considered
De Alemedia 2012 (2010) [142] Spain	Home ventilation: $91,704 (£101,997) per annum Home renovations: $5,676 (£6,314): (lifetime cost)	Caregiver lost wages: $7,008 (£7,671) per annum
Moss et al 1996 (1995) [154] United States	Ventilation in hospital: $366,852 (£401,570) per annum Home ventilation: $136,852 (£149,804) per annum	Not considered

Currency conversions were undertaken using data from the International Monetary Fund (IMF) [115] and costs were inflated using the Hospital and Community Health Services (HCHS) pay and prices index [116].

2.3.4 Health state utilities

Eleven studies included the use of health state utility values (HSUVs), of which 6 [119-123] took their values from Kiebert et al. [155] who elicited utilities based on standard gamble using structured interviews in the UK. However, this study is limited in size, with only 77 MND patients involved and with some health states being represented by as few as 15 patients. Two other studies used hypothetical utility values which were not based on any empirical evidence but rather, intended for illustrative purposes [127,128]. One study estimated utilities using the standard gamble technique administered to a panel of healthcare professionals with experience of treating patients with MND [126]. A study in Spain used postal administration of the EQ-5D-3L and EQ-Visual Analogue Scale (VAS) in a sample of 36 patients [146]. The most recent utility study, which was

set in the UK with a sample of 214 patients, also used the EQ-5D-3L along with the EQ-VAS, to elicit utilities longitudinally [156].

Studies which included HSUVs varied in their description of health states. A five-stage model was used in Kiebert et al. [119-124,155] based on the earlier work of Rivere et al. [157]. The full definitions of health states are presented in Box 1. Jones et al. [156] used the King's ALS clinical stage framework consisting of five states; stage 1: diagnosis and involvement of 1st region, stage 2: involvement of 2nd region, stage 3: involvement of 3rd region, stage 4: need for intervention (gastrostomy or non-invasive ventilation) and stage 5: death. Ackerman et al [126] used a five state model defined by Appel ALS scores which cover aspects of speech, respiratory function, swallowing, dressing and feeding, need for assistive device, work status and medical care. By contrast Ringel et al [127] used a four health stage model based solely on forced vital capacity scores (FVC). López-Bastida et al. [146] used a simple two-stage classification of the disease with patients either in the mild state (not in need caregiver help), and the severe state (in need of caregiver help).

Health state utility data in the economic evaluations came from a limited number of sources [15-20,22], with some reliant on hypothetical data [127,128] highlighting a lack of evidence in this area (Table 3). Furthermore, as descriptions of health states are not uniform [119-124,126,127], utility values varied significantly, especially in some progressively low functional states. In the most recent UK evaluations [120-124], the terminal state value is 0.45, compared with -0.53 in the study by Ackerman et al [126]. Differences in health utility values appear to be more divergent than the health descriptions used in these evaluations [126,157].

Box 1. Health states as defined by Rivere et al. [157].

State 1 (mild). Recently diagnosed; mild deficit in only 1 of 3 regions (i.e., speech, arm, and leg); and functionally independent in speech, upper extremity activities of daily living, and ambulation.

State 2 (moderate). Mild deficit in all 3 regions or moderate to severe deficit in 1 region, while the other 2 regions are normal or mildly affected.

State 3 (severe). Needs assistance in 2 or 3 regions; speech is dysarthric and/or patient needs assistance to walk and/or needs assistance with upper extremity activities of daily living.

State 4 (terminal). Non-functional use of at least 2 regions and moderate or non-functional use of the third region.

2.3.5 Uncertainty analysis

Most economic evaluations considered parameter uncertainty by application of one-way sensitivity analysis around benefits/utilities [120-126,128] (n=9), costs [120-124,129] (n=6) and tolerance of patient cohorts to treatment [119]. Three studies performed two-way sensitivity analysis to jointly assess the contribution of both costs and benefits/utilities on cost-effectiveness [120-122], while only one study carried out a full probabilistic sensitivity analysis [127]. Scenario analyses considered uncertainty in costs, health benefits and survival [125,130] (n=2). Two studies attempted to account for structural uncertainty with alternative models [123,125], while another study assessed the impact of different patient demographics on cost-effectiveness (of riluzole) [130]. Uncertainty analysis in the studies showed that the main drivers of cost effectiveness in MND treatments were drug costs and estimated extension in survival.

2.4 Discussion

With the prospect of new treatments for MND on the horizon, including the neuroprotective agent edaravone, tyrosine kinase inhibitor masitinib and gene and stem cell therapies [163-166], there will be an increased need for robust data and modelling framework to assess their cost-effectiveness. Most economic evaluations are based on Markov models with disease-specific stages which aim to trace disease progression and its effects on patients and their use of healthcare resources. The often used five-stage disease progression model [119-124,155,157] has methodological issues with respect to its clinical classification system of health states. It conflates recency of diagnosis with severity of illness and would lead to some patients being misplaced in health states which may not reflect the true costs or benefits related to their disease status. It therefore fails to meet the Markov assumption of mutual exclusivity. The Kings ALS clinical staging model, as used in Jones et al. [156], provides health state descriptions which are mutually exclusive, and therefore potentially making it more appropriate for use in Markov modelling.

Costs can vary considerably between stages of MND [133,146,151]. However, only a few studies have reported disease stage specific costs. Munsat et al. [151] is the most cited among UK economic evaluations, but the estimates from this analysis are based on resource utilization taken from interviews with four neurologists with experience of treating MND, and needs updating. The authors highlight the variation in cost estimates between each expert, reflecting differences in clinical practice. Economic evaluations included in our review did not consider changes to the annual costs of standard palliative care by disease stage as it was claimed that these would be unaffected by treatment. This assumption has been untested empirically.

Several studies have reported or estimated indirect costs associated with MND [119,126,127,129,133,134,136--138,140-142,145,146,153,154]. While there are recognised

challenges relating to the measurement of lost productivity by both patients and their caregivers [167-169], the importance is more so in MND as patients have a higher earning potential than the national averages [140], owing to the average age of onset peaking around the mid-fifties and the fact that the disease presents more in men [108].

Instruments used to measure the health related quality of life in patients with MND need to be sensitive enough to capture changes across the disease course, have the required dimensions which apply to the condition and robust psychometric properties. The EQ-5D-3L has been used as a generic measure, but concerns have been highlighted over its ability to record an accurate representation of the complexity surrounding quality of life (QoL) in MND. The narrow conceptual components of the EQ-5D-3L often restricts utility measurement and fails to include symptom characteristics which are salient to those with MND, such as respiratory function and communicative ability [170,171]. Issues such as sensitivity of the EQ-5D-3L to clinical changes in the disease course and their resulting impact on utilities, and floor effects further limit the usefulness of the instrument. One undertaking which could help in this regard is using the EQ-5D-5L, which improves the range of responses and mitigates the floor effects to some degree [172,173].

The ALS Utility Index is a disease-specific instrument which has been developed through surveying a general population sample, but is yet to be validated in MND patients [174]. This index also focuses solely on the physical functioning aspect of MND, with no domain for emotional wellbeing or pain. In spite of its drawbacks, it represents an advance that should prompt further research in this area.

Patients' preferences may vary with respect to the management of the different symptoms experienced. Direct utility estimation in MND has been limited to the standard gamble approach. Kiebert et al. [155] found that utility scores, based on standard gamble, were higher for disease stage 3 (needs assistance in two or three regions) than disease stage 2 (mild defect in three regions) in the ALS Health State Scale; despite the descriptions of disease stage 3 appearing to be significantly worse. However, when the same sample of patients completed the EQ-5D-3L questionnaire, the results showed a progressive lowering of health stage utilities along the disease course. Furthermore, this study elicited significantly different utility score estimations for standard gamble and EQ-5D-3L methods. The standard gamble results from this study featured in the riluzole manufacture's submission to National Institute for Health and Care Excellence (NICE) [122], as well as the more recent economic evaluations in MND [119-123]. Alternative methods of direct utility estimation, such as time trade off or the use of choice-based techniques such as the Discrete Choice Experiment (DCE), have hitherto not featured in MND studies.

MND has important and significant impacts on informal caregivers, such as family members [175-177]. While there is debate concerning the inclusion of the QoL effects on carers in economic evaluations, and methodological challenges relating to the measurement, valuation and incorporation of QoL impacts on carers [167-169], the lack of consideration for carer utilities in MND is apparent. Further challenges include consideration of how carers' productivity is affected by the disease, especially in the latter stages of the condition when more help is required. The inclusion of caregiver utilities in a cost-effectiveness framework for MND could affect conclusions of economic evaluations of treatments if those treatments are near cost-effectiveness threshold values, as was the case for riluzole, and prove to impact on carers' QoL [167].

The strengths of the review are in its inclusiveness and in-depth analysis of the methods and findings from economic and cost of illness studies. We are unaware of any other review of the economic evidence in MND, but acknowledge some unpublished articles such as HTA reports in jurisdictions outside the UK may have been omitted. We excluded non-English studies, which may have been available to European, Latin American and Asian reimbursement authorities (for instance in relation to riluzole).

The challenges presented in this review highlight the current methodological limitations faced by health economists in MND. These issues, such as the need to incorporate the broader impact of treatments on patients' QoL and the uncertainty surrounding the current empirical evidence, transcend into other disease areas, notably multiple sclerosis and dementia [178,179]. This would indicate that the issues pertinent to the economic analysis of MND treatments are far reaching, and require due consideration in other health economic work.

2.5 Conclusion

Current economic studies in MND are limited in many ways, including the comprehensiveness and reliability of cost studies, a lack of research reporting health state utilities across the disease course, and poorly defined health states. Our review has highlighted a clear need for up to date and methodologically rigorous economic data for unbiased assessment of the cost-effectiveness of future interventions in MND. We have also identified a need for a robust evaluation framework in MND. Future research should target these limitations, and utilise data from large, longitudinal studies, such as the UK Trajectories of Outcome in Neurological Conditions (TONiC) study [6], which has recruited over 800 patients to complete cost and quality of life questionnaires. Improvements in economic studies in MND will result in more informative guidance on healthcare resource allocation when new, and inevitably expensive, interventions are licensed.

Preface to Chapter three

The previous chapter has highlighted the limited evidence base in health economic aspects of MND. This shows that there are high levels of uncertainty associated with the key parameters required to carry out health economic evaluations of new treatments for MND.

Chapter three aims to add to the limited evidence by providing a statistical link from the most commonly used MND specific measure used in clinical trials, the ALSFRS-R, and a commonly used generic preference-based measure, the EQ-5D-5L. The EQ-5D is not commonly collected in MND trials, therefore if a mapping algorithm can be demonstrated to be able to accurately predict EQ-5D utilities from the ALSFRS-R, this could provide a valuable link and address some of the gaps in evidence highlighted by the previous chapter.

Chapter three

Mapping ALSFRS-R and ALSUI to EQ-5D in patients with motor neurone disease

Abstract

Background: The Amyotrophic Lateral Sclerosis Functional Rating Scale-revised (ALSFRS-R) is the preferred measure of health outcome in clinical trials in motor neurone disease (MND). However it does not provide a preference-based health utility score, required for estimating QALYs in economic evaluations for health technology assessments.

Methods: Direct mapping models were developed using Ordinary Least Squares (OLS) and Tobit regression analyses to estimate EQ-5D-5L utilities (based on English tariffs) with ALSFRS-R total, domain and item scores used as explanatory variables, using patient-level data from a UK cohort study. Indirect mapping models were also used to map EQ-5D-5L domains, using the same variables, along with the Neuropathic Pain Scale (NPS) and Hospital and Anxiety Depression Scale for MND (MND-HADS) using multinomial logistic regression analysis. Goodness-of-fit was assessed along with predicted values for each mapping model.

Results: The best performing model predicting EQ-5D-5L utilities used 5 items of the ALSFRS-R items as explanatory variables in a stepwise OLS regression. The mean squared error was 0.0228, and the absolute mean error was 0.1173. Prediction was good, with 55.4% of estimated values within 0.1 and 91.4% within 0.25 of the observed EQ-5D-5L utility value. Indirect mapping using the NPS and HADS provided less predictive power than direct mapping models.

Conclusion: This is the first study to present mapping algorithms to 'crosswalk' between ALSFRS-R and EQ-5D-5L. This analysis demonstrates that the ALSFRS-R can be used to estimate EQ-5D-5L utilities when they have not been collected directly within a trial.

3.1 Introduction

Motor Neurone Disease (MND) (also known as Amyotrophic Lateral Sclerosis, ALS) is a progressively degenerative neurological condition, which affects the motor neurones in the brain and spinal cord. Life expectancy is between 3 to 5 years from symptom onset [180] and quality of life (QoL) is greatly impaired. Established treatments are symptom management, riluzole which increases median survival by about 3 months [181], and palliative care [182].

The recent approval of edaravone [10] by the US Food and Drug Administration (FDA) and the development of other new treatments options [63,165] will increase the need for evidence to support health technology assessment (HTA) and reimbursement decisions. At present, there is limited literature on preference-based health utilities in patients with MND [183], which are required for the calculation of quality-adjusted life-years (QALYs) for cost-utility analyses.

The EuroQoL EQ-5D is the preferred measure of the National Institute for Health and Care Excellence (NICE) [184] for calculating QALYs and the most widely used generic preference-based health outcomes measure, facilitating comparisons of health technologies between different diseases [185]. However, concerns have been expressed in applying this measure to MND patients, as it does not account for a range of symptoms, including communication, fatigue, swallowing and respiratory difficulty [180]. Previous experience of the EQ-5D-3L version in patients with MND, is that the measure can be used but with cautions of ceiling/floor effects, amongst other issues [186,187].

When EQ-5D data are not available, NICE allows for utilities be estimated by mapping from other health-related QoL measures [188]. A number of studies concerned with mapping disease-specific QoL instruments to the EQ-5D have been published [189] and guidelines produced for best practice [190,191]. Mapping from a non-preference based measure to the EQ-5D can be performed by predicting either the EQ-5D health utility values (direct mapping) or each of the five domain responses (indirect mapping). However, there is limited use of either approach in the context of neurological conditions [192,193].

The Amyotrophic Lateral Sclerosis Functioning Rating Scale-Revised (ALSFRS-R) [194] is recommended for use in clinical trials of treatments for MND [195] to capture clinical changes in areas of motor, bulbar and respiratory function. While this is not a preference-based measure, the ALS Utility Index, which is derived from 5 items of the ALSFRS-R and based on US general population tariff scores, does allow for utilities to be estimated [196], but has not been used in MND patients.

The aim of our study is to develop algorithms for mapping, both directly and indirectly, from measures used in MND clinical studies to allow for future prediction of EQ-5D-5L utility in populations of MND patients where utility data have not been collected.

3.2 Methods

3.2.1 Data

Data were sourced from the on-going Trajectories of Outcomes in Neurological Conditions (TONiC) study [6]. This longitudinal study of QoL and economic outcomes includes a large cohort of patients with MND recruited throughout the UK. Participants complete a series of outcome measures and provide demographic and clinical information.

For the analysis, we used baseline responses from a cross-section of patients recruited by MND clinical and research teams up to January 2017, who were at different stages of the disease course. Cross-sectional rather than longitudinal data were used as only 106 from 636 patients had returned any follow-up questionnaires at the time of analysis for this paper. All questionnaires used in the mapping analysis were returned in a single pack which the participant was requested to complete on the same day if possible. Clinicians allocated MND to limb, bulbar or respiratory onset types and performed disability assessment using the ALSFRS-R.

Ethical approval was granted from NRES Committee North West - Greater Manchester West (reference number 11/NW/0743).

3.2.2 Missing data

Mapping was only conducted for participants for whom complete data were available. A logistic regression was used to test whether participants who had returned incomplete questionnaires were comparable to those who had fully completed questionnaires, in terms of their age, gender, MND onset type, independent completion of questionnaires and recruiting centre.

3.2.3 Measures

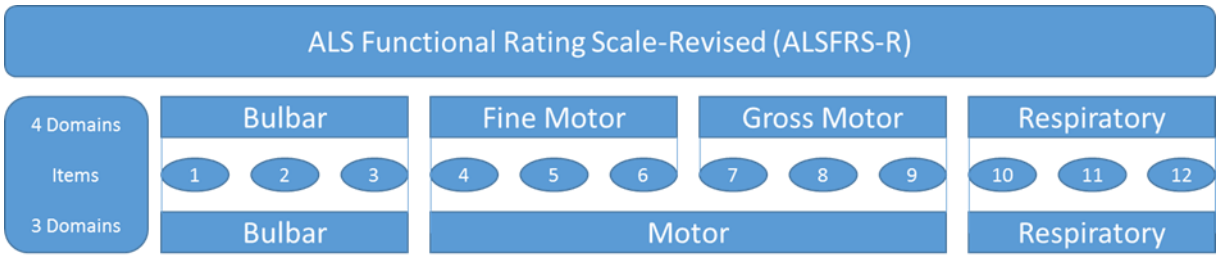
The EQ-5D-5L was included in the TONiC study to estimate health utilities. It covers the health domains of mobility, self-care, usual activities, pain and anxiety/depression, each with five levels of severity [197]. A preference-based single index score can be generated with any combination of responses, anchored at 0 to represent death, 1 representing full health and, based on an English tariff, includes the worst health state of -0.281. These health utility values have been developed using general public responses to a standard gamble survey.

Three measures were selected from the TONiC dataset for the purposes of mapping to EQ-5D-5L:

1) ALSFRS-R, from which the ALS Utility Index was derived

The revised version of the ALSFRS incorporates respiratory items, increasing the sensitivity of the instrument to changes in the disease course of MND [194]. The ALSFRS-R is a validated MND-specific 12-item questionnaire, concerning bulbar, limb and respiratory function. Responses range from a score of 0 (severe problems) to 4 (no change). Responses to the ALSFRS-R are often used to derive a single index value and this value is reported in many clinical studies, but recent evidence suggests that the ALSFRS-R should be examined on a domain level, to generate either 3 or 4 domain scores to overcome concerns of unidimensionality [198] (Figure 3.1).

Figure 3.1 – Structure of ALSFRS-R, showing breakdown by 4 and 3 domains and items



Bulbar items are related to speech and communication. The fine motor domain is concerned with actions such as hand and finger movements, whereas gross motor captures changes in areas such as walking and climbing. The respiratory domain captures issues around the ease of breathing.

The ALS Utility Index is derived from the following ALSFRS-R domains: speech and swallowing, eating and self-care, leg function and respiratory function [196]. Preference weights were generated from members of the general public in the US using the standard gamble method and can be used to calculate a single preference-based utility score for persons with MND.

2) Neuropathic Pain Scale (NPS)

The Neuropathic Pain Scale [199] measures the intensity, unpleasantness and sharpness of neuropathic pain. The questionnaire consists of 10 scales with varying descriptions of pain, each with a possible response value between 0 (no pain) and 10 (worst pain imaginable). A further item concerns the length of time the patient has experienced pain with a score of between 0 and 2. Responses to the scales and the time item are summed to provide an NPS index score.

3) Hospital and Anxiety Depression Scale for MND (MND-HADS)

The MND-HADS [200] is a modified version of the Hospital and Anxiety Depression Scale (HADS) [201], developed for use in MND populations to address concerns that items in the original HADS may be confounded by physical disability. The modified HADS-A and HADS-D, which have acceptable psychometric properties, resulted from the removal of one item from both 7-item scales.

3.2.4 Statistical methods

With our aim of developing a crosswalk between the selected measures available in the TONiC study and the EuroQoL EQ-5D-5L, we tested a variety of model types and structures to arrive at a preferred model, and present alternative acceptable models that may suit different scenarios depending on data availability. Models based on direct mapping to EQ-5D-5L utilities (based on the English tariff [197]) and indirect mapping to EQ-5D-5L domains were tested. We randomly divided our dataset into estimation and validation samples in a 2:1 ratio, allowing algorithms generated in the estimation sample to predict values in the validation sample.

For the direct mapping analysis, we considered the ALSFRS-R by individual items, 3 and 4 domains variables and index score (Table 3.1; Figure 3.1). Individual item responses to the ALSFRS-R provide the greatest granularity; domain variables of the ALSFRS-R offer more concise information on distinctive features of MND [194], and the index score was selected based on it being reported in many clinical studies in MND. The ALSUI was analysed by index score only as this measure is preference-based and therefore the index value combined weighted domain responses.

Two model types were chosen for the direct mapping. Firstly, we used ordinary least squares (OLS) regression which has been used extensively in comparable studies with acceptable performance [189]. Given that EQ-5D-5L utility data are skewed, however, violating the assumption of normality, and are censored at the upper limit of 1, we also used a Tobit regression model [202], and compared the results with OLS regressions models.

For all indirect mapping analyses, we used multinomial logistic regression to account for the categorical nature of EQ-5D domains, and the ordering of EQ-5D domain levels (Table 1). Initially, we used the same combinations of explanatory variables as in our direct mapping analysis. We then undertook a second indirect mapping analysis, which included the additional measures of the NPS and MND-HADS. These were included to overcome the lack of pain and mental health domains within the ALSFRS-R, therefore aiding our indirect mapping analysis. All models, direct and indirect, were run with and without the demographic variables of age, gender and MND onset type. All regression analyses were performed on the estimation sample, with generated results used to

predict values using the validation sample. Furthermore a stepwise selection was used to examine if a reduced ALSFRS-R item model was more appropriate, in regards to removing variables whose coefficients were not rationally directed, and to test if a more efficient model could be obtained.

Data management was carried out using Microsoft Excel (Microsoft, Washington, USA) and R statistical software version 3.0 (Vienna, Austria) [203] was used for statistical analysis.

Table 3.1 - Mapping models used in statistical analysis

Model number	**Explanatory variables**	**Statistical methods**
Direct Mapping		
1a	ALSFRS-R Index	OLS and Tobit
1b	ALSFRS-R Index and demographics	OLS and Tobit
2	ALSFRS-R 4 Domains	OLS and Tobit
3	ALSFRS-R 3 Domains	OLS and Tobit
4	ALS Utility Index	OLS and Tobit
5	ALSFRS-R items	OLS and Tobit
6	Stepwise ALSFRS-R items	OLS and Tobit
Indirect mapping		
7	ALSFRS-R Index	Multinomial Logistic
8	ALSFRS-R 4 Domains	Multinomial Logistic
9	ALSFRS-R 3 Domains	Multinomial Logistic
10	ALS Utility Index	Multinomial Logistic
11	ALSFRS-R items	Multinomial Logistic
12	Stepwise ALSFRS-R items	Multinomial Logistic
13	ALSFRS-R index score, NPS and MND-HADS	Multinomial Logistic
14	ALSFRS-R 4 domains, NPS and MND-HADS	Multinomial Logistic
15	ALSFRS-R 3 domains, NPS and MND-HADS	Multinomial Logistic
16	ALSUI score, NPS and MND-HADS	Multinomial Logistic
17	ALSFRS-R items, NPS and MND-HADS	Multinomial Logistic
18	ALSFRS-R Items stepwise selection, NPS and MND-HADS	Multinomial Logistic

3.2.5 Assessing Model Performance

Model performance was examined by the mean squared errors (MSE) and mean absolute errors (MAE), in line with mapping guidance [184,190], to identify the best predictive models. For

optimal model selection, we used MSE results from our validation sample. The MAE was included to complement the MSE analysis and ensure that models selected based on a lower MSE score also had a lower MAE score.

Tests of systematic bias in selected models, chosen by lowest MSE score, were performed by examining the percentage of predicted values which deviated from observed values by more than 0.10 and 0.25. In order to identify if the selected models performed better for particular ranges of utility values, we also present the errors for the following categories of EQ-5D-5L utility scores: <0, 0 to <0.2, 0.2 to <0.4, 0.4 to <0.6, 0.6 to <0.8, 0.8 to 1. The plotting of histograms of the residuals of observed and predicted values of the selected model provided visual evidence of the nature of errors present in the models. Examination of mean differences in utility values between data sets was also undertaken. Finally, the Akaike Information Criterion (AIC) [204] was used to test the fit of models with lowest MSE for each of the explanatory variable groups in the direct mapping and also for all indirect mapping models.

The conduct and reporting followed guidance from the MApping onto Preference-based measures reporting Standards (MAPS) statement [190].

3.3 Results

3.3.1 Data Characteristics

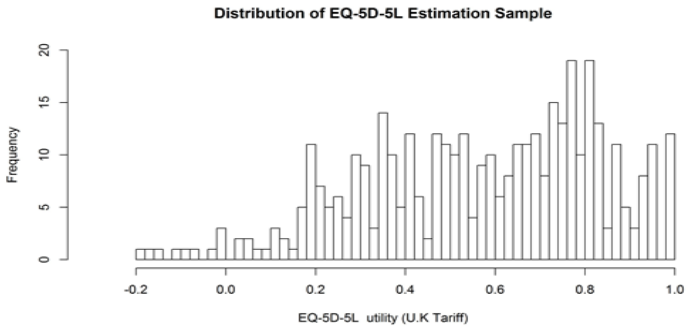
Questionnaires were posted to 958 patients. A response rate of 66.4% for our cross-sectional data set was achieved, resulting in 636 returned questionnaires. 41 were incomplete for direct mapping, leaving a total of 595 completed patient questionnaires for inclusion in this analysis. Respondents who did not fully complete questionnaires were not statistically different from those who returned completed questionnaires, with respect to the variables tested (supplementary appendix 3). For the direct mapping, 397 patients were randomly assigned to the estimation sample and 198 to the validation sample. For indirect mapping, 18 patients had not completed the required additional questionnaires, therefore 385 patients were in the estimation sample and 192 in the validation sample. Estimation and validation samples were well balanced in terms of age, gender split, MND onset type (bulbar, limb and respiratory), severity of EQ-5D domain responses, their EQ-5D-5L and ALSUI utility values, and ALSFRS-R, NPS and MND-HADS scores (Tables 2 and 3). The mean age of respondents was 65.1 years, which is in line with reported average ages of MND patients, while the gender split of 61% male is also reflected within the literature [205].

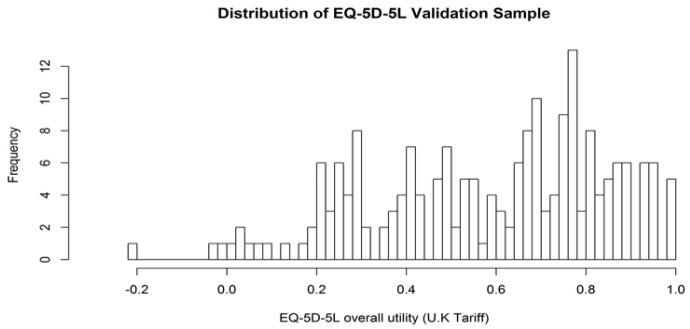
Table 3.2 – Patient characteristics

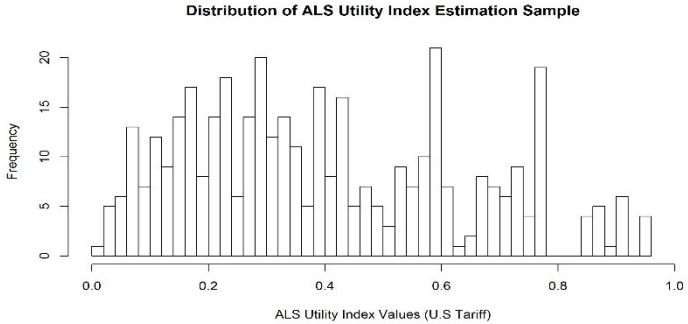
Characteristic	**Whole sample** (n=595)	**Estimation sample** (n=397)	**Validation sample** (n=198)
Demographics			
Male n (%)	363 (61.0)	243 (61.2)	120 (60.6)
Age mean (SD)	65.07 (10.89)	65.25 (10.89)	64.70 (10.6)
MND Onset n (%)			
Limb	404 (69.9)	265 (66.8)	139 (70.2)
Bulbar n (%)	159 (26.7)	112 (28.2)	48 (26.7)
Respiratory n (%)	11 (2.5)	8 (2.0)	3 (2.5)
Measures mean (SD)			
EQ-5D-5L index	0.57 (0.26)	0.57 (0.26)	0.58 (0.27)
EQ-5D VAS	0.60 (21.30)	0.61 (22.01)	0.60 (21.78)
ALSFRS-R score	31.95 (8.33)	31.85 (8.13)	32.15 (8.73)
ALS Utility Index	0.40 (0.24)	0.40 (0.24)	0.41 (0.24)
Neuropathic Pain Scale	30.02 (16.40)	28.74 (16.95)	32.62 (15.01)
MND-HADS	8.02 (5.45)	7.90 (5.51)	8.25 (5.32)

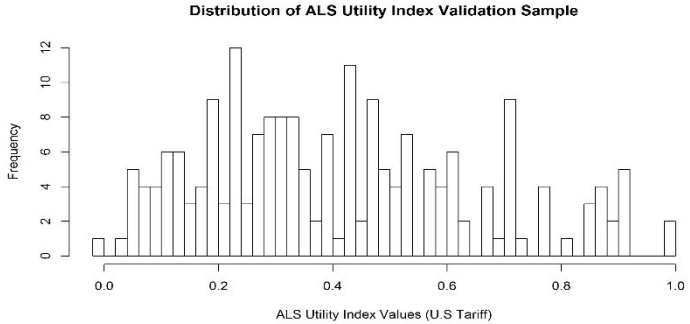
Figure 3.2 shows the distributions of the EQ-5D-5L utilities, ALSFRS-R index values and ALSUI scores in both samples. The number of individuals reporting negative EQ-5D-5L in our full dataset was 13 (2.2%). EQ-5D-5L utility ranged from -0.21 to 1, whereas the ranges of other measures were: ALSFRS-R (1 to 48), ALSUI (0 to 1), NPS (0 to 85) and MND-HADS (0 to 28)

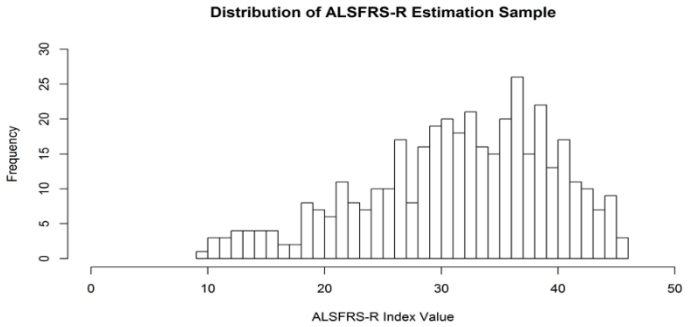
Figure 3.2 - Distributions of EQ-5D-5L utilities, ALSFRS-R Index scores and ALSUI scores by sample

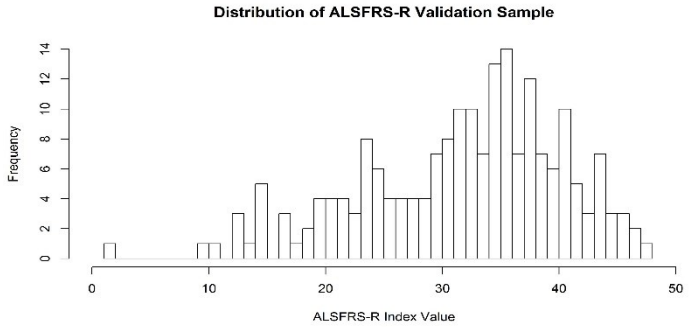









Distribution of ALSFRS-R Estimation Sample
Frequency
0
5
10
15
20
25
30
0
10
20
30
40
50
ALSFRS-R Index Value


Distribution of ALSFRS-R Validation Sample
Frequency
0
2
4
6
8
10
12
14
0
10
20
30
40
50
ALSFRS-R Index Value

The distributions of responses varied across the EQ-5D domains (Table 3), with mobility and usual activities associated with greater proportions of severe problems, compared to other domains, reflecting the impact of MND upon patients' motor functioning. There were fewer responses in the more severe categories of pain/discomfort, with 5 (0.8%), and anxiety/depression with 6 (1.0%) individuals reporting severe problems.

Table 3.3 - Distribution of responses by EQ-5D-5L domains

EQ-5D Domain	**Whole Sample** (n=595)	**Estimation Sample** (n=397)	**Validation Sample** (n=198)
Mobility	n (%)	n (%)	n (%)
Level 1	99 (16.6)	63 (15.9)	36 (18.2)
Level 2	81 (13.2)	54 (13.6)	27 (17.6)
Level 3	157 (26.4)	106 (26.4)	52 (26.3)
Level 4	152 (25.6)	100 (25.2)	52 (26.3)
Level 5	106 (17.8)	75 (18.9)	31 (15.7)
Self-care			
Level 1	118 (19.8)	85 (21.4)	33 (16.7)
Level 2	152 (25.6)	88 (22.2)	64 (32.3)
Level 3	162 (27.2)	110 (27.7)	52 (26.3)
Level 4	71 (11.9)	52 (13.1)	19 (9.6)
Level 5	92 (15.5)	62 (15.6)	30 (15.2)
Usual Activities			
Level 1	53 (8.9)	35 (8.8)	18 (9.1)
Level 2	117 (19.7)	71 (17.9)	46 (23.2)
Level 3	174 (29.2)	118 (29.7)	56 (28.3)
Level 4	118 (19.8)	85 (21.4)	33 (16.7)
Level 5	115 (22.4)	88 (22.2)	45 (27.7)
Pain/discomfort			
Level 1	179 (30.1)	116 (29.2)	63 (31.8)
Level 2	213 (33.8)	140 (35.3)	73 (36.9)
Level 3	161 (27.1)	114 (28.7)	47 (23.7)
Level 4	37 (3.6)	22 (5.5)	15 (7.6)
Level 5	5 (0.8)	5 (1.3)	0 (0.0)
Anxiety/depression			
Level 1	268 (45.1)	181 (45.6)	87 (43.9)
Level 2	203 (34.1)	131 (33.0)	72 (36.4)
Level 3	98 (16.5)	66 (16.6)	32 (16.2)
Level 4	20 (3.3)	15 (3.8)	5 (2.3)
Level 5	6 (1.0)	4 (1.0)	2 (1.0)

3.3.2 Model Performance

The results of our mapping analysis by model type are presented in Table 4. Patient demographics were significant predictors of EQ-5D-5L utilities in only model OLS 1b; results for the other models with demographic variables are therefore not presented.

Direct mapping

Direct mapping models were compared in terms of their fitted values deviating by more than 0.1 and 0.25 of the true utility. This ranged from 31.3% to 55.4% for within 0.10 of true value; and 56.3% and 91.4% within 0.25. Direct mapping models generally performed well in estimating mean utility in the estimation sample, with all models predicting the mean correctly to 2 decimal places. In the validation sample, however, only three mapping models predicted the mean to 2 decimal places, and only three predicted negative utility values. Model OLS (5) demonstrated the lowest MSE (0.0245), MAE (0.1218) and AIC values in the validation sample; however it contained non-significant coefficients, and negative (counterintuitive) coefficients on items 1 to 4, and 12. For these reasons, among direct mapping models the use of the reduced ALSFRS-R item model with stepwise selection of explanatory variables (model OLS (6)) is preferred. While MSE (0.0228), MAE (0.1173) and AIC all indicated model OLS (6) to provide the best fit of the data, the predicted errors were not uniform across the range of EQ-5D-5L utility scores (Table 4). Larger errors were apparent for negative utilities and for utilities in the range of 0 to 0.2. Figure 3.3 presents the fitted versus observed values, and Figure 3.4 plots the residuals. The model was strongest when predicting values from 0.2 to 0.8. 91.7% of estimations were within 0.25 of the observed EQ-5D-5L values, with 55.4% within 0.10 of the true value. The algorithm generated from this regression is presented below:

EQ-5D-5L utility = 0.086203 + 0.057486*item6 + 0.046674*item7 + 0.058688*item8 + 0.035927*item9 + 0.021126*item10s

Figure 3.3 – Selected model OLS (6) fitted values v observed values, full sample

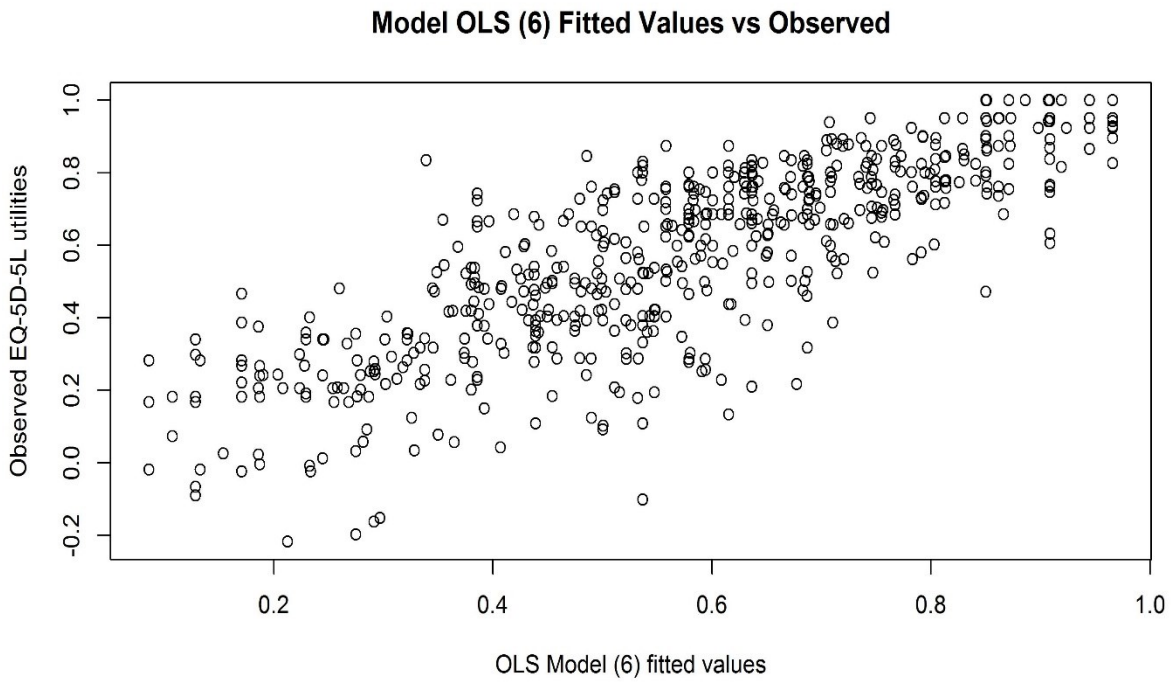
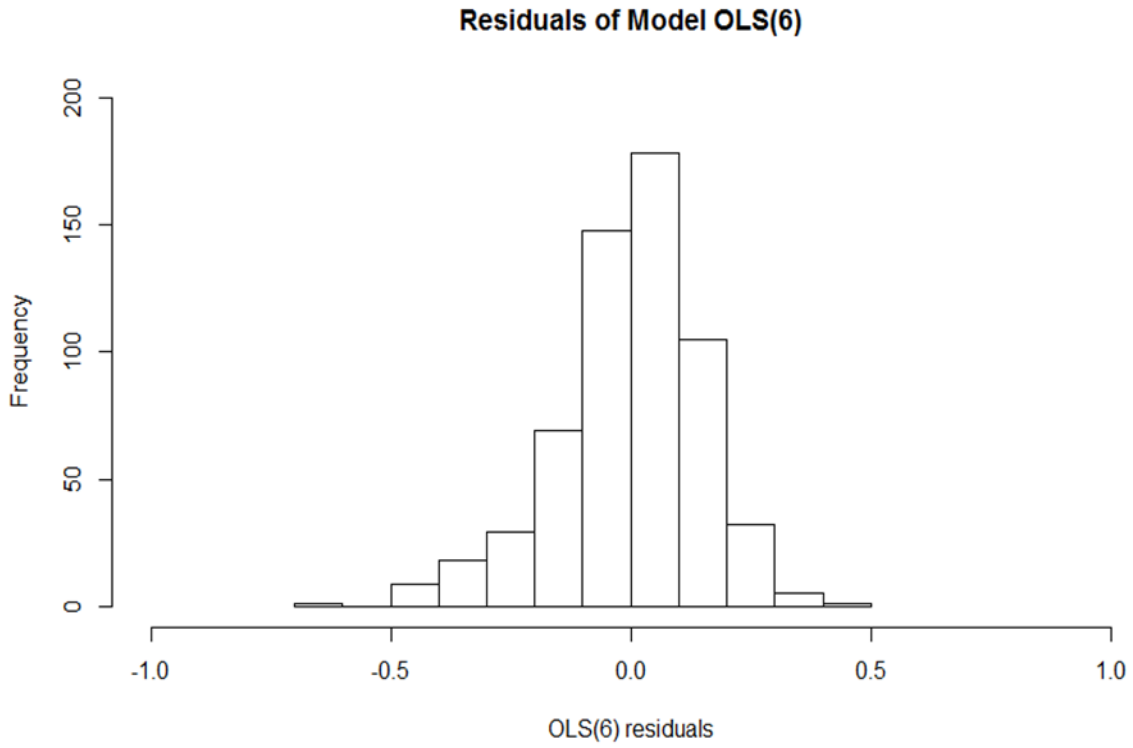


Figure 3.4 - Residuals of selected model OLS (6), based on the full sample



Indirect mapping

All indirect mapping models using the ALSFRS-R or ALSUI were upwardly biased as they consistently predicted higher utility values. They reported higher MSEs and MAEs than the direct

mapping models using the same clinical information, but while the use of the additional measures of the NPS and MND-HADS resulted in lower errors, these models did not outperform direct mapping models.

To researchers who may benefit from our mapping analysis, and recognising that data availability may differ from one study to another, we present the complete results of the best performing models for various levels of information required in the supplementary appendix 4.

Table 3.4 – Mapping results

Model	**Estimation Sample (n=397)**				**Validation Sample (n=198)**			
	Mean (SD)	Min, Max	MSE	MAE	Mean (SD)	Min, Max	MSE	MAE
Observed EQ-5D-5L utility	0.57 (0.26)	-0.2, 1	N/A	N/A	0.58 (0.26)	-0.21, 1	N/A	N/A
Direct Models								
OLS (1)	0.57 (0.19)	0.1, 0.86	0.0404	0.1594	0.57 (0.18)	-0.06, 0.9	0.037	0.1552
OLS (1b)	0.57 (0.19)	0.04, 1	0.0339	0.1448	0.57 (0.19)	-0.06, 1	0.0306	0.1407
OLS (2)	0.57 (0.21)	0.08, 0.96	0.0239	0.1202	0.57 (0.15)	0.1, 0.96	0.0461	0.1794
OLS (3)	0.57 (0.20)	0.05, 0.94	0.0447	0.1245	0.57 (0.15)	0.08, 0.94	0.0281	0.1306
OLS (4)	0.57 (0.16)	0.03, 0.92	0.0219	0.1201	0.57 (0.16)	0.3, 0.95	0.0441	0.1731
OLS (5)	0.57 (0.22)	0.09, 0.98	0.0224	0.1135	0.57 (0.22)	0.1, 0.98	0.0245	0.1218
OLS (6)	0.57 (0.21)	0.09, 0.96	0.0221	0.1112	0.58 (0.21)	0.1, 0.97	0.0228	0.1173
Tobit (1)	0.57 (0.17)	0.09, 0.87	0.0405	0.1589	0.59 (0.18)	-0.06, 0.91	0.0371	0.1545
Tobit (1b)	0.57 (0.19)	0.05,0.99	0.0356	0.1453	0.57 (0.20)	-0.01,0.92	0.0310	0.1423
Tobit (2)	0.57 (0.17)	0.07, 0.85	0.0421	0.1625	0.51 (0.15)	0.03, 0.81	0.0466	0.1801
Tobit (3)	0.57 (0.21)	0.03, 0.97	0.0271	0.1283	0.55 (0.20)	0.01, 0.92	0.0280	0.1329
Tobit (4)	0.57 (0.16)	0.3, 0.93	0.0447	0.1711	0.58 (0.16)	0.3, 0.97	0.0442	0.1730
Tobit (5)	0.57 (0.22)	0.08, 1	0.0219	0.1132	0.57 (0.22)	0.09, 0.99	0.0255	0.1288
Tobit (6)	0.57 (0.21)	0.08, 0.9	0.0233	0.1149	0.57 (0.21)	0.09, 0.98	0.0250	0.1241
Indirect								

Models								
Mlogit (7)	0.65 (0.24)	0.17, 0.95	0.5660	0.1794	0.66 (0.23)	0.17, 1	0.0597	0.1812
Mlogit (8)	0.66 (0.22)	0.17, 1	0.0390	0.1285	0.67 (0.58)	0.17, 1	0.0320	0.1415
Mlogit (9)	0.64 (0.24)	0.17, 1	0.0360	0.1379	0.60 (0.25)	-0.02, 1	0.0303	0.1342
Mlogit (10)	0.61 (0.23)	0.17, 1	0.0501	0.1811	0.62 (0.22)	0.17, 0.95	0.0510	0.1732
Mlogit (11)	0.62 (0.21)	0.01, 0.95	0.0274	0.1165	0.62 (0.22)	-0.02, 1	0.0315	0.1526
Mlogit (12)	0.61 (0.22)	0.01, 0.95	0.0252	0.1140	0.62 (0.21)	-0.02, 1	0.0310	0.1563
Mlogit (13)	0.57 (0.22)	-0.07, 1	0.0199	0.1034	0.58 (0.22)	-0.02, 1	0.0308	0.1310
Mlogit (14)	0.72 (0.23)	0.34,1	0.0989	0.2421	0.58 (0.21)	0.17,1	0.0534	0.2181
Mlogit (14)	0.74 (0.22)	0.49, 0.93	0.0954	0.2339	0.60 (0.21)	0.34, 0.94	0.0663	0.2316
Mlogit (15)	0.59 (0.23)	0.09, 1	0.1581	0.1581	0.59 (0.22)	-0.02, 1	0.0497	0.1757
Mlogit (16)	0.49 (0.22)	-0.09, 1	0.1870	0.1870	0.51 (0.11)	0.51, 1	0.0657	0.1956
Mlogit (17)	0.59 (0.22)	-0.1, 1	0.2010	0.2010	0.59 (0.21)	0.17, 1	0.0441	0.2301

3.4 Discussion

Our study provides evidence that the ALSFRS-R, conceptually, could be a good candidate for mapping to the EQ-5D-5L in MND patients as the domain themes which appear in the EQ-5D (pain and anxiety/depression) but not in the ALSFRS-R, are reported in less severe terms in MND patients. This may partially explain why our mapping results fell within the reported MSE ranges of other mapping studies [189], and allowed us to assert that mapping from the ALSFRS-R to the EQ-5D-5L is viable.

The various ALSFRS-R mapping models showed markedly better predictive results than the models using the ALSUI when estimating EQ-5D-5L utilities. This may be in part due to the use of US preference tariff in the ALSUI, contrasting with our use of the English EQ-5D-5L tariff given the population from which the data were derived; but also the different selection of ALSFRS-R domains in their construct. The ALSUI estimated utility from items 1, 6, 8, 10 and 12 of the ALSFRS-R, whereas our best fitting model, OLS (6) used items 6 to 10. More research is needed to confirm the external validity of the ALSUI, and the extent to which it can be used to complement generic preference-based measures. Based on our mapping analysis, we cannot recommend using this measure to crosswalk to the EQ-5D-5L in MND patients. Table 5 outlines strengths of each mapping strategy.

Table 3.5 – Mapping guidance listed by strength of recommendation

Information available	**Model to use**	**Notes**
ALSFRS-R item responses	OLS (6)	OLS (5) can also be used if all ALSFRS-R items are to be included regardless of negative, non-intuitive coefficients
ALSFRS-R domain scores	OLS (3)	This models uses 3 domains of the ALSFRS-R
ALSFRS-R index score with demographic data	OLS (1b)	Age, gender and MND onset type information needed for this model
ALSFRS-R index score	OLS (1)	Caution has been noted when using the index score of the ALSFRS-R. This should only be considered if domains or item scores are not available
ALSFRS-R index score, Neuropathic Pain Scale and MND-HADS	Mlogit (13)	This models requires three questionnaires, and should only be used if researchers do not want to use the English EQ-5D-5L tariff

As with the majority of previous mapping studies, our analysis found OLS regressions to have the strongest predictive power, slightly bettering the results from the Tobit regressions for direct mapping [189]. Indirect mapping models with the same specifications as the direct models showed higher MSEs using a multinomial logistic regression and consistently estimated larger mean EQ-5D utilities compared to observed values. The addition of the NPS and HADS to the indirect models reduced reported MSEs, but not to the extent as estimated in the direct mapping models. Demographic information did not significantly improve predictive power of the models, with the exception of model 1b; this result has been reflected in other MND research [206].

Our preferred model OLS (6), using a selection of ALSFRS-R items as explanatory variables, had MSE and MAE values comparable to other neurological statistical mapping work [192,193], and to errors reported in mapping studies in general [189]. The fact that our most accurate model, in terms of lowest MSE, contained only 5 items from the 12 item ALSFRS-R highlights the limitations of the use of the EQ-5D-5L within MND populations. There are characteristics of the disease, as defined by the main disease-specific measure in MND, that do not influence the metric of EQ-5D-5L health utility. These are: communication, salivation, swallowing, hand use, and respiratory function.

This study is a useful addition to the literature, in that it presents results for both direct and indirect mapping algorithms, using a variety of model structures. Few previous mapping studies have carried out both approaches on the same dataset [189]. Ours is the first study, to our knowledge, to have carried out such an analysis within an MND population, and provides useful evidence for the development of economic analyses in MND where EQ-5D data have not been collected directly. A strength of the analysis was the completeness of returned questionnaires with no evidence that data were not missing at random.

Our analysis may have been more robust, however, if we had access to data for a greater number of patients. In being a longitudinal study, TONiC offered the opportunity for an analysis of repeated measures to increase the power of the study, but as only 106 (of 636 patients) had returned at least 1 follow-up questionnaire pack at our cut-off date, we considered this to be an insufficiently representative sample for such an analysis. TONiC nonetheless represents both the largest and one of the most detailed quality of life studies for MND in the world. The strongest models within this study were unable to predict negative utility values for patients with MND, and had a higher error rate for low utility scores. This is of concern as MND is associated with relatively low utility values reflecting very poor health-related quality of life, although our data had only a few patients reporting negative utilities (2.2%). The mapping algorithms presented in this study were validated

from a sample of data which stems from the same study. While this is commonplace in the literature [189-191], external validation would have been preferable in the context of assessing broader generalisability. Finally, it should be noted that directly collected data on EQ-5D-5L utilities always supersedes predicted values based on mapping algorithms.

3.5 Conclusion

Many studies in MND have not used preference-based utility measures, which are required increasingly to support health technology assessment and reimbursement decisions. The algorithms presented here provide an option for estimating EQ-5D-5L utility when this has not been collected directly from MND patients. This study has shown that it is possible to predict, with reasonable accuracy (based on reported MSE ranges for other mapping studies), EQ-5D-5L utility values from the ALSFRS-R. It is also possible to map indirectly to EQ-5D-5L domains if the NPS and MND-HADS have been used alongside the ALSFRS-R. These findings should aid health technology assessment of interventions for MND, by providing evidence linking commonly used clinical outcome measures to a widely adopted generic preference-based measure, the EQ-5D-5L.

Preface to Chapter four

The previous chapter has shown that it is possible to estimate EQ-5D-5L utilities from the commonly used MND disease-specific measure, the ALSFRS-R. While this is a useful link, mapping is not the preferred method by which to include health utilities in health economic evaluations. The ideal scenario is the use of EQ-5D values which are directly collected using that measure. Preferably this should be collected as part of any clinical trial. However, in many cases this information is not available. In these situations, health utilities can be taken from the literature, if a relevant study can be found in which the appropriate measurement (usually EQ-5D for NICE submissions) has been used in a patient population which is generalisable to the population under consideration. Further to this, information on disease specific costs is needed to carry out health economic evaluations, as incremental cost differences between treatment options is needed. As a minimum, relevant costs from a health payer (such as the NHS) perspective should be reported, in order to meet the NICE reference case requirement.

Chapter four aims to provide health state utilities and costs by well accepted MND specific health stage models. This will add to the limited evidence base to date and investigate how these two key parameters vary over the course of MND.

Chapter four

Health utilities and costs for Motor Neurone Disease

Abstract

Background: Motor Neurone Disease (MND) places a significant burden on patients, their carers and healthcare systems. However, there is limited information on health utilities and costs within a United Kingdom setting.

Methods: Patients with MND, recruited via 22 regional clinics, completed a postal questionnaire of a cost and quality of life survey. Health outcome assessment included the EQ-5D-5L, EQ-VAS, ALS Utility Index and the Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised. Clinical staging was based on the Kings and MiToS systems. The questionnaire asked about patients' use of primary, secondary and community care services in the previous 3-months. Variability in total costs was examined using regression models.

Results: 595 patients were included in the health utility analysis, of whom 584 patients also completed a resource use questionnaire. Mean health utility decreased and costs increased between consecutive Kings stages, from 0.76 (95%CI 0.71, 0.80) and £1,096 (£757, £1,240) in Kings stage 1, to 0.50 (0.45, 0.54) and £3,311 (£2,666, £4,151) in stage 4, respectively. The changes by MiToS stages, were from 0.71 (0.69, 0.73) and £1,115 (£937, £1,130) in MiToS stage 0, to 0.25 (0.07, 0.42) and £2,899 (£2,190, £3,840) in stage 2. Kings stages 3 and 4, and MiToS Stages 1 and 2, respectively, were significant in explaining variability in total costs.

Conclusions: The impact of MND on health utilities and costs differs by disease severity. The data provided here can be used in cost-effectiveness analyses and to inform decision-making regarding healthcare provision for people with MND.

4.1 Introduction

Motor Neurone Disease (MND) (or amyotrophic lateral sclerosis) is a neurodegenerative condition associated with extensive impairment of patients' mobility, communication and breathing which results in large reductions in their health-related quality of life [180]. The average life expectancy is only 3-5 years from disease onset [207], and treatment is focused on symptom management, slowing disease progression and providing palliative care. MND incurs significant financial burden on patients, caregivers and health-care providers [86].

Economic studies in MND, including cost analyses, preference elicitation and economic evaluations, both in the UK and internationally, have a limited evidence base. The extent of these limitations has been described in previously [183]. These studies are restricted in terms of cost measurement, and small samples for estimating health utility. There is limited experience of the EuroQoL (EQ)-5D in MND populations [155,156], with possible flooring effects in the EQ-5D-3L. In one study [156], EQ-5D-3L health utility values decreased as disease severity increased, whereas in the other, health states were not mutually exclusive [151].

The costs of MND to the National Health Service (NHS) in the UK are believed to be high, owing to the nature of the disease, but are not well documented within the health economic literature [183]. A study published in 1998, using expert opinion to estimate resource use, provided cost estimates for some less severe health stages which were higher than the most severe stage [208]. In international studies, reported costs have increased as severity worsened [183].

Previous studies in MND have involved attempts to describe and model disease progression using clinical staging systems [209-212]. These facilitate analyses of costs and benefits using clearly defined clinical health states, and provide a structure for simulation models, such as Markov models [213], for estimating cost-effectiveness. The two most commonly used clinical staging systems in MND are the Kings [211] and the Milano-Torino (MiToS) staging systems [212]. The Kings system is structured around clinical involvement of bulbar and limb areas and nutritional or respiratory failure, whereas the MiToS system is focused on loss of independence across the domains of bulbar, gross motor, fine motor and respiratory function.

The Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised (ALSFRS-R) [214] is the most commonly used disability measure in MND clinical research and is recommended for capturing changes in functionality along the disease course [215,216]. The Kings system was developed for patients to be staged by clinicians but it can also be derived from the ALSFRS-R with good accuracy [217], whereas the MiToS staging system is based directly on ALSFRS-R responses. The fact that both of these staging systems can be used with ALSFRS-R data makes them particularly useful in the analysis of clinical trials, which routinely use the ALSFRS-R as a primary outcome measure.

We aimed to contribute to the evidence-base of economic studies in MND by presenting costs, and health state utilities based on the EQ-5D-5L [218] and the ALS utility index [219], defined by both Kings and MiToS staging. This study provides evidence for future economic evaluations in MND to inform health technology assessment and decision making within the UK National Health Service. We provide valuable information on how MND impacts upon patients' quality of life and NHS costs at various clinical stages, by using a range of health measures, and two clinical staging models.

4.2 Methods

4.2.1 Data

Data were obtained from the Trajectories of Outcomes in Neurological Conditions (TONiC) study conducted in the UK. TONiC is an ongoing longitudinal cohort study which, at the time of this study, had recruited patients from 22 MND clinics within the UK. The TONiC study is primarily aimed at assessing factors affecting patients' quality of life and their experience of MND [6]. Patients attending MND clinics are given questionnaires at various time points for postal return; at 0, 4, 9, 14, 18, 27 and 60 months from their inclusion in the TONiC study. The health economic components include a resource use questionnaire, which was a modified version of a questionnaire used in epilepsy [220] (available from the Database of Instruments for Resource Use Measurement [221]) and the EQ-5D-5L questionnaire. Baseline responses were used in the present study as longitudinal data had not matured sufficiently at the time of analysis, which resulted in this study being cross-sectional in nature.

The TONiC study was approved in the UK by NRES Committee North West – Greater Manchester West (reference number 11/NW/0743) and informed consent was obtained from the patients involved.

Demographic and clinical characteristics

Respondents reported their age and gender. MND onset type (limb, bulbar, respiratory or unknown) was determined by a clinician familiar with each patient's case.

Disease-specific measure

The ALSFRS-R, which was completed by study participants, comprises of 12 items, each scored from 0 (worse state) to 4 (best state with less disability) [214]. These items are commonly divided to 3 distinct domains; bulbar (items 1-3), motor (items 4-9) and respiratory (items 10-12) [222]. We used the ALSFRS-R to assign patients to Kings and MiToS states [211,212].

4.2.2 Health utility

Patents completed the EQ-5D-5L which comprises of five domains; mobility, self-care, usual activities, pain/discomfort, and anxiety/depression [218]. Each of these domains has five levels indicating worsening health, from having no problems, to having severe problems. Responses to the EQ-5D-5L were used to calculate health utilities. Each possible combination of responses to the five questions of the EQ-D5-5L is associated with a health utility value, based on time trade-off valuations from a representative sample of the general public in England [218]. We also present results from the EQ-5D-visual analogue scale (EQ-5D VAS), which complements the main EQ-5D-5L questionnaire and measures self-reported health values as indicated on a vertical scale.

The ALS Utility Index (ALSUI) was calculated from responses to the ALSFRS-R [219]. This measure is the first such to present a disease-specific, preference-based index in MND, based on scoring determined from a standard gamble experiment taken by members of the general public in the United States. The ALSUI algorithm attaches a preference weighting to ALSFRS-R items 1, 6, 8, 10 and 12, to obtain a single index value ranging from 0 (worse possible state) to 1 (best possible state) [219].

4.2.3 Clinical staging

As Kings staging is based on clinical observation, we used a mapping algorithm which estimates Kings stages with 92% accuracy [217]. Kings stages 1,2,3 are allocated by counting the number of times a patient shows any loss (any score below 4 on relevant items) in the domains of bulbar, upper limbs and lower limbs; involvement of any one region leads to stage 1, two regions stage 2 and so on. Patients with respiratory or swallowing failure are allocated to stage 4.

We also allocated patients in this study to MiToS system stages [212]. This was done using the ALSFRS-R, from which the MiToS system was developed. All MiToS stages are allocated on counts of losses in independence in domains of bulbar, gross motor, fine motor and respiratory function. Loss of independence in one domain is stage 1, in two domains stage 2 and so on. If no loss of independence has occurred, patients are allocated to stage 0.

4.2.4 Resource use and cost

The resource use questionnaire asked respondents about their use of NHS resources, including medicines, primary and community care, hospital clinic visits and inpatient stays, tests and investigations, within the previous 3 months. Unit costs were sourced from NHS reference costs [223] and the Personal Social Services Research Unit (PSSRU) [224,225]. All costs were inflated to 2017 values, where applicable, using the hospital and community health services (HCHS) index PSSRU [224]. The full disaggregated data on items and unit costs are presented in the Supplementary Appendix 5.

4.2.5 Missing data

Patients were omitted from the analysis of health utility if they had not completed the EQ-5D-5L in full, and from the cost analysis if they had not answered all required questions on the resource use questionnaire. Further to this, patients who did not complete the ALSFRS-R in full were also excluded from the analysis, as they could not be staged according to the Kings or MiToS staging systems.

4.2.6 Statistical analysis

95% Confidence intervals (CI) were estimated using non-parametric bootstrapping, with 2000 replications with replacement to account for the skewed nature of cost and health utility data. Generalized Linear Models (GLM) with a Gamma log link were used to estimate the influence of certain variables, including disease staging, on total patient costs. Data

management was undertaken in Excel 2016 (Microsoft, Washington, United States) and all analyses were carried out in R (Vienna, Austria) [226].

4.3 Results

4.3.1 Description of data

958 patients received posted questionnaires, of which 636 (66.4%) were returned. Forty-one of the questionnaires returned were not sufficiently completed. Health utility data were therefore available from 595 patients, and of these 584 patients also provided cost information, meaning cost data were available for 98.1% of patients who were staged. Table 1 presents the characteristics of the participants for both health utility and cost analyses. The 11 patients who had completed EQ-5D-5L and ALSFRS-R questionnaires, but had failed to complete the resource use questionnaire, had comparable characteristics to those who had completed all three questionnaires. Patients in the sample were of similar age, gender distribution and MND onset type, to those previously reported in MND populations [227].

Table 4.1 – Characteristics of samples used for the health utility and cost analysis

		Health utility sample	**Cost sample ***
Sample size		595	584
Age in years	Mean (SD)	65.07 (10.89)	65.05 (10.91)
Female	n (%)	232 (39.0)	230 (39.21)
Months since diagnosis	Mean (SD)	26.54 (38.8)	26.59 (38.9)
MND Onset Type	n (%)		
Limb		404 (69.9)	400 (68.5)
Bulbar		159 (26.7)	155 (26.5)
Respiratory		11 (2.5)	11 (1.9)
EQ-5D-5L Utility	Mean (95% CI) Median (IQR)	0.57 (0.55, 0.59) 0.61 (0.38, 0.78)	0.57 (0.55, 0.59) 0.62 (0.38, 0.79)
EQ-5D VAS	Mean (95% CI) Median (IQR)	60 (58, 62) 60 (45, 75)	60 (58, 62) 61 (45, 75)
ALSFRS-R Index	Mean (95% CI) Median (IQR)	31.95 (31.19, 32.55) 33 (27, 38)	31.96 (31.16, 32.58) 33 (27, 38)
ALS Utility Index	Mean (95% CI) Median (IQR)	0.40 (0.38, 0.42) 0.36 (0.27, 0.58)	0.40 (0.38, 0.42) 0.36 (0.27, 0.59)
Kings Staging	n (%)		
Stage 1		89 (15.0)	86 (14.7)
Stage 2		135 (22.7)	131 (22.4)
Stage 3		206 (34.6)	201 (34.4)
Stage 4		162 (27.3)	160 (27.4)
MiToS Staging	n (%)		
Stage 0		301 (50.59)	296 (50.69)
Stage 1		198 (33.28)	195 (33.39)
Stage 2		73 (12.69)	72 (12.33)
Stage 3		18 (3.03)	16 (2.74)
Stage 4		5 (0.84)	5 (0.86)

4.3.2 Health utility by MND stage and disease onset type

Table 2 shows the distributions of EQ-5D-5L domains by model and health state. The "usual activities" EQ-5D-5L domain was most affected by MND, as it had the highest proportion of severe (level 5) responses and any problems (levels 2-5) across all clinical stages. Conversely, the least affected domain on the EQ-5D-5L questionnaire was "anxiety/depression" across all clinical stages, based on the same metrics, with the exception of patients in MiToS stage 3.

Table 4.2 – EQ-5D-5L domain responses by health stage and system

	EQ-5D-5L domain				
Response Level	**Mobility**	**Self-Care**	**Usual Activities**	**Pain/Discomfort**	**Anxiety/Depression**
Full sample (N= 595)	n (%)	n (%)	n (%)	n (%)	n (%)
Level 1	99 (16.6)	118 (19.8)	53 (8.9)	179 (30.1)	268 (45.0)
Level 2	81 (13.6)	152 (25.6)	117 (19.7)	213 (35.8)	203 (34.1)
Level 3	157 (26.4)	162 (27.2)	174 (29.2)	161 (27.1)	98 (16.5)
Level 4	152 (25.5)	71 (11.9)	118 (19.8)	37 (6.2)	20 (3.4)
Level 5	106 (17.8)	92 (15.5)	133 (22.4)	5 (0.9)	6 (1.0)
Some Problems	496 (83.3)	477 (80.2)	542 (91.1)	416 (69.9)	327 (55.0)
Kings stage 1 (N= 89)					
Level 1	49 (55.1)	42 (47.2)	25 (28.1)	46 (51.7)	53 (59.5)
Level 2	7 (7.9)	23 (25.8)	27 (30.3)	26 (29.2)	29 (32.6)
Level 3	12 (13.5)	16 (17.98)	16 (18.0)	16 (18.0)	6 (6.7)
Level 4	15 (16.9)	6 (6.4)	11 (12.4)	1 (1.1)	1 (1.1)
Level 5	6 (6.7)	2 (2.2)	10 (11.3)	0 (0)	0 (0)
Some Problems	40 (44.9)	63 (52.8)	64 (72.0)	43 (48.3)	36 (40.4)
Kings stage 2 (N= 135)					
Level 1	22 (16.3)	28 (20.7)	11 (8.2)	43 (31.9)	66 (48.9)
Level 2	28 (20.7)	40 (29.6)	33 (24.4)	47 (34.8)	45 (33.3)
Level 3	37 (27.4)	34 (25.2)	44 (32.6)	33 (24.4)	16 (11.9)
Level 4	26 (19.3)	16 (11.9)	28 (20.7)	10 (7.4)	5 (3.7)
Level 5	21 (15.6)	16 (11.9)	18 (13.3)	1 (0.74)	2 (1.5)
Some Problems	113 (83.7)	107 (79.3)	124 (91.9)	92 (68.1)	69 (51.1)
Kings stage 3 (N= 206)					
Level 1	6 (2.9)	22 (10.7)	6 (2.9)	43 (20.9)	86 (41.7)
Level 2	30 (14.6)	57 (27.7)	36 (17.5)	76 (36.9)	75 (36.4)
Level 3	66 (32.0)	65 (31.6)	66 (32.0)	72 (35.0)	39 (18.9)
Level 4	63 (30.6)	31 (15.0)	47 (22.8)	11 (5.4)	3 (1.5)
Level 5	40 (19.5)	30 (14.6)	50 (24.3)	3 (1.5)	2 (1.0)
Some Problems	200 (97.1)	184 (89.3)	200 (97.1)	163 (79.06)	120 (58.3)
Kings stage 4 (N= 162)					
Level 1	19 (11.7)	24 (14.8)	9 (5.6)	45 (27.8)	61 (37.7)
Level 2	17 (10.5)	31 (19.1)	21 (13.0)	61 (37.7)	53 (32.7)
Level 3	40 (24.7)	46 (28.4)	48 (29.6)	40 (24.7)	35 (21.6)
Level 4	48 (29.6)	18 (11.1)	31 (19.1)	15 (9.3)	11 (6.8)
Level 5	38 (23.5)	43 (26.5)	53 (32.7)	1 (0.6)	2 (1.2)
Some Problems	143 (88.3)	138 (85.2)	153 (94.4)	117 (72.2)	101 (62.4)

MiToS stage 0 (N= 301)					
Level 1	79 (26.3)	94 (31.2)	46 (15.3)	113 (37.5)	154 (51.2)
Level 2	54 (17.9)	119 (39.5)	96 (31.9)	102 (33.8)	107 (35.6)
Level 3	96 (31.9)	75 (24.9)	101 (33.6)	71 (23.6)	35 (11.6)
Level 4	88 (29.2)	13 (4.3)	39 (13.0)	14 (4.6)	5 (1.7)
Level 5	6 (2.0)	0 (0)	22 (7.3)	1 (0.3)	0 (0)
Some Problems	222 (73.4)	207 (68.8)	255 (84.7)	188 (62.5)	147 (48.8)
MiToS stage 1 (N=198)					
Level 1	16 (8.9)	22 (11.1)	9 (4.6)	40 (20.2)	84 (42.4)
Level 2	22 (11.1)	26 (13.1)	16 (8.1)	75 (37.9)	63 (31.8)
Level 3	44 (22.2)	60 (30.3)	60 (30.3)	66 (33.3)	37 (18.7)
Level 4	60 (30.3)	41 (20.7)	57 (28.8)	14 (7.1)	7 (3.5)
Level 5	54 (27.3)	47 (23.7)	54 (27.3)	1 (0.5)	3 (1.5)
Some Problems	182 (91.9)	176 (88.9)	189 (95.5)	158 (80.0)	114 (57.6)
MiToS stage 2 (N= 73)					
Level 1	4 (5.5)	3 (4.1)	1 (1.4)	21 (28.8)	24 (32.9)
Level 2	5 (6.9)	4 (5.5)	5 (6.9)	26 (35.6)	29 (39.7)
Level 3	11 (15.1)	21 (28.8)	10 (13.7)	15 (20.6)	15 (20.6)
Level 4	17 (23.3)	15 (20.6)	19 (26.0)	8 (11.0)	4 (5.5)
Level 5	36 (49.3)	36 (49.3)	38 (52.1)	3 (4.1)	1 (1.4)
Some Problems	69 (94.5)	70 (95.9)	72 (98.6)	52 (71.2)	49 (67.1)
MiToS stage 3 (N=18)					
Level 1	0 (0)	0 (0)	0 (0)	4 (22.2)	3 (16.7)
Level 2	1 (5.6)	2 (11.1)	1 (5.6)	7 (38.9)	5 (27.8)
Level 3	3 (16.7)	5 (27.8)	2 (11.1)	6 (33.3)	8 (44.4)
Level 4	7 (38.9)	1 (5.6)	2 (11.1)	1 (5.6)	2 (11.1)
Level 5	7 (38.9)	10 (55.6)	13 (72.2)	0 (0)	0 (0)
Some Problems	18 (100)	18 (100)	18 (100)	14 (77.8)	15 (83.3)
MiToS stage 4 (N= 5)					
Level 1	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Level 2	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Level 3	1 (20)	1 (20)	1 (20)	1 (20)	2 (40)
Level 4	2 (40)	0 (0)	0 (0)	1 (20)	1 (20)
Level 5	2 (40)	4 (80)	4 (80)	3 (60)	2 (40)
Some Problems	5 (100)	5 (100)	5 (100)	5 (100)	5 (100)

‘Some problems’ are defined as any response from level 2 to level 5

Mean (95% CI) health utility scores for the entire sample were EQ-5D-5L 0.57 (0.55, 0.59), EQ-5D VAS score 60 (58, 62), and ALS utility Index 0.40 (0.38, 0.42). EQ-5D-5L health utility decreased with increasing clinical severity across both the Kings and MiToS systems. For Kings staging, health utility reduced from 0.76 (95% CI 0.71, 0.80) in stage 1, to 0.50 (0.45, 0.54) in stage 4 (Table 3). In the MiToS staging, mean health utility of stage 0 was 0.71 (95% CI 0.69, 0.73) but reduced to 0.25 (0.07, 0.42) in stage 4. The measures of ALSFRS-R total score, ALSFRS-R domains, ALSUI and EQ-5D VAS all reduced through progressively worse clinical stages. ALS utility index values were much lower for all stages across both systems than the values for EQ-5D-5L. This result was more prominent for the most severe states in both models, with Kings stage 4 mean EQ-5D-5L health utility at 0.50 (0.45, 0.54) and ALSUI at 0.24 (0.21, 0.27); and MiToS stage 4 EQ-5D-5L health utility of 0.25 (0.07, 0.42) and ALSUI utility of 0.07 (0.07, 0.08).

Table 4.3 - Mean EQ-5D-5L utility, ALSFRS-R and ALS Utility Index by stage and MND onset type

	EQ-5D-5L Utility	**EQ-5D VAS**	**ALSFRS-R Index**	**ALSFRS-R Bulbar**	**ALSFRS-R Gross Motor**	**ALSFRS-R Respiratory**	**ALS Utility Index**
	Mean (95% CI)						
Full Sample	0.57 (0.55,0.59)	60 (58,62)	31.95 (31.19,32.55)	8.43 (8.13,8.69)	13.67 (13.16,14.07)	9.85 (9.61,32.55)	0.40 (0.38,0.42)
Kings staging							
Stage 1	0.76 (0.71,0.80)	72 (68,76)	40.90 (40.56,41.94)	10.48 (9,63,10.85)	19.98 (18.79,20.81)	11.44 (11.24,11.58)	0.63 (0.60,0.68)
Stage 2	0.60 (0.56,0.64)	63 (59,66)	35.68 (35.25,37.03)	10.33 (10.09,10.79)	14.38 (13.44,15.24)	11.02 (10.92,11.35)	0.50 (0.46,0.54)
Stage 3	0.53 (0.50,0.56)	59 (57,62)	30.54 (29.89,31.58)	8.09 (7.77,8.41)	11.91 (11.56,12.76)	10.49 (10.30,10.69)	0.35 (0.33,0.37)
Stage 4	0.50 (0.45,0.54)	52 (48,56)	24.42 (25.16,25.65)	5.85 (5.21,6.49)	11.53 (10.62,12.48)	7.04 (6.57,7.68)	0.24 (0.21,0.26)
MiToS staging							
Stage 0	0.71 (0.69,0.73)	68 (66,70)	37.39 (36.89,37.98)	9.19 (8.89,9.52)	17.26 (16.85,20.31)	10.97 (10.83,11.11)	0.56 (0.54,0.58)
Stage 1	0.48 (0.44,0.51)	55 (52,58)	29.59 (28.85,30.31)	8.49 (7.98,8.98)	11.21 (10.31,11.94)	9.89 (9.52,10.22)	0.30 (0.28,0.32)
Stage 2	0.36 (0.31,0.42)	49 (43,54)	21.44 (20.21,22.67)	6.75 (5.85,7.60)	8.23 (7.12,9.42)	6.43 (5.74,7.18)	0.16 (0.13,0.18)
Stage 3	0.33 (0.23,0.43)	47 (37,58)	15.17 (13.61,16.83)	3.57 (2.39,4.78)	5.50 (3.83,7.33)	6.11 (4.61,7.61)	0.08 (0.06,0.11)
Stage 4	0.25 (0.07,0.42)	45 (22,70)	9.40 (5.1,12.6)	2.00 (0.6,3.6)	3.40 (1,5.8)	4.00 (2,6)	0.07 (0.03,0.09)

Scale range of included measures (minimum to maximum): EQ-5D-5L -0.21 to 1; EQ-5D VAS 0 to 1; ALSFRS-R Index 0 to 48; ALSFRS-R Bulbar 0 to 12; ALSFRS-R Gross Motor 0 to 24; ALSFRS-R Respiratory 0 to 12; ALS Utility Index 0 to 1.

EQ-5D-5L health utility tended to be higher with bulbar onset MND at 0.68 (95% CI 0.64, 0.72), compared to either limb 0.53 (0.49, 0.57) or respiratory onset, 0.53 (0.35, 0.71) (Supplementary Appendix 5). This was despite the mean ALSFRS-R total score being higher in patients with limb onset MND in our study than in patients with bulbar onset.

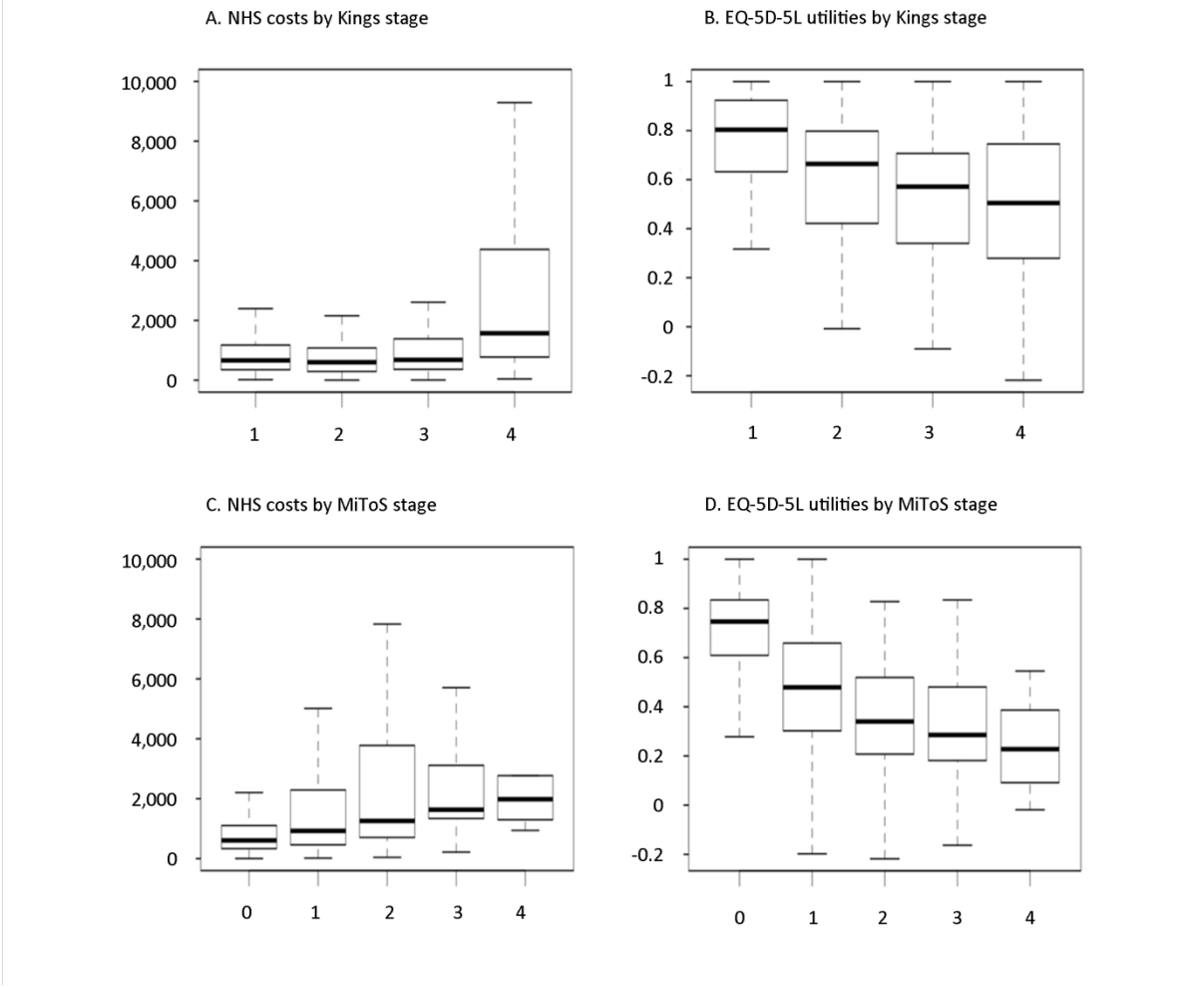
4.3.3 Resource use and costs by MND stage and disease onset type

Seventy-seven (13.2%) patients experienced at least one inpatient stay during a 3-month period (Table 4). Inpatient stays were most frequent in Kings stage 4 (0.45) and MiToS stage 1 (0.40). Kings stage 4 was associated with more resource use in all categories compared with other stages, except tests and investigations. The mean number of home visits by doctors and nurses was higher for Kings stage 4 (0.68 and 4.35, respectively) than other Kings stages; higher levels of home care were also evident in patients in MiToS stage 4 (15.2 nurse home visits and 2.2 doctor home visits) than in less severe MiToS stages (ranging between 0.61 and 5.38 nurse home visits, and 0.43 and 1.17 doctor home visits).

The total costs per patient over a 3-month period were £1,889 (95% CI £1,596, £2,214), ranging from £53 to £39,884 (Table 4.5; Figure 4.1). Overnight inpatient stays made up 35.8% of total costs, making it the single largest cost category, while community costs contributed 14.2% of total costs.

Kings stages showed progressively higher mean costs with advancing disease, ranging from £1,096 (95% CI £757, £1,240) in stage 1 to £3,311 (£2,666, £4,151) in stage 4 (Figure 4.1). The association of MiToS staging with costs was less clear, with patients categorised in stage 0 having the lowest cost of £1,115 (£937, £1,130) and stages 1 to 4 having higher costs, with the highest cost occurred in stage 2 at £2,889 (£2,190, £3,810). Drug costs were also higher for Kings stage 4 than other Kings stages; and lower for stage 0 than other stages based on MiToS stages. Secondary care costs were higher than primary care costs for patients in all states, with the exception of those in MiToS stage 4. Bulbar onset patients had higher costs in every cost category compared to other onset types.

Figure 4.1- Utilities and costs by health stage system and stages, shown with box plots



Parts A and B show costs and utilities, respectively, by Kings staging system whereas parts C and D show the same information for MiToS staging system

Generalized Linear Model regressions indicated that Kings stages 3 and 4, and MiToS Stages 1 and 2, respectively, were significant in explaining variability in total costs (Table 6). Bulbar onset was associated with higher costs in the MiToS system, but neither age nor gender contributed significantly to costs in either model.

4.3.4 Comparison of Kings and MiToS staging

There was moderate correlation (Spearman's rank coefficient of 0.58), in patient categorisation between the Kings and MiToS staging systems (Supplementary Appendix 5). Within any given Kings stage, health utility scores decreased with increasing MiToS stage. For example, patients in Kings stage 4 had mean health utility scores ranging from 0.25 (MiToS stage 4) to 0.67 (MiToS Stage 1).

Table 4.4 - Resource use by health stage and system
Abbreviations: CT Computerised Tomography; MRI Magnetic Resonance Imaging; EMG Electromyography

			Kings stage				MiToS stage				
Resource Category	**Units; Number of**	**Full Sample**	1	2	3	4	0	1	2	3	4
		Mean, (maximum value) – all min values = 0									
Primary Care											
Nurse GP Surgery	Visits	0.48 (20)	0.39 (4)	0.53 (10)	0.26 (5)	0.77 (20)	0.48 (10)	0.54 (20)	0.30 (6)	0.50 (2)	2.2 (10)
Doctor GP Surgery	Visits	0.88 (10)	0.90 (8)	0.89 (10)	0.75 (8)	1.03 (10)	1.05 (10)	0.83 (10)	0.58 (6)	0.50 2)	1.6 (6)
Nurse at Home	Visits	1.95 (90)	0.53 (10)	0.99 (90)	1.32 (25)	4.35 (90)	0.61 (15)	1.78 (25)	6.25 (90)	5.38 (24)	15.2 (28)
Doctor at Home	Visits	0.30 (12)	0.08 (2)	0.13 (5)	0.20 (12)	0.68 (10)	0.04 (3)	0.43 (12)	0.63 (10)	1.17 (8)	2.2 (8)
Secondary Care											
Casualty Department	Visits	0.24 (10)	0.13 (8)	0.17 (7)	0.28 (10)	0.33 (8)	0.18 (8)	0.31 (10)	0.40 (10)	0.17 (1)	0.00 (0)
Nurse Outpatient	Visits	0.96 (18)	0.65 (4)	0.58 (6)	0.78 (10)	1.68 (18)	0.71 (10)	1.29 (18)	1.10 (12)	1.61 (10)	0.40 (1)
Doctor Outpatient	Visits	2.11 (31)	2.05 (21)	2.32 (21)	2.06 (31)	2.12 (21)	2.17 (31)	2.19 (31)	1.31 (12)	3.00 (12)	1.80 (3)
Ambulance Use	Call outs	0.25 (12)	0.04 (2)	0.23 (6)	0.25 (12)	0.37 (10)	0.1 0 (12)	0.27 (10)	0.60 (6)	0.11 (1)	0.00 (0)
Inpatient Stays	Number of admissions	0.23 (12)	0.08 (2)	0.17 (10)	0.15 (12)	0.45 (10)	0.10 (4)	0.40 (12)	0.34 (5)	0.11 (1)	0.20 (1)
Tests											
Blood	Tests	1.16 (12)	1.11 (6)	0.97 (6)	0.39 (10)	0.75 (10)	1.10 (6)	1.04 (12)	1.54 (18)	1.00 (3)	0.40 (2)

Urine	Tests	0.11 (5)	0.04 (3)	0.04 (2)	0.13 (4)	0.19 (5)	0.06 (2)	0.14 (4)	0.21 (5)	0.33 (2)	1.20 (1)
Ultrasound	Scans	0.06 (3)	0.08 (3)	0.05 (2)	0.05 (2)	0.08 (2)	0.04 (1)	0.09 (3)	0.10 (3)	0.11 (1)	0.00 (0)
X-ray	Scans	0.18 (6)	0.15 (2)	0.15 (3)	0.19 (5)	0.22 (6)	0.14 (3)	0.21 (5)	0.30 (6)	0.11 (1)	0.00 (0)
CT Scan	Scans	0.12 (10)	0.13 (2)	0.13 (2)	0.10 (2)	0.13 (10)	0.12 (2)	0.16 (3)	0.05 (2)	0.00 (0)	0.00 (0)
MRI Scan	Scans	0.20 (6)	0.21 (2)	0.25 (3)	0.23 (6)	0.11 (2)	0.23 (2)	0.20 (3)	0.15 (6)	0.00 (0)	0.00 (0)
EMG	Scans	0.26 (3)	0.33 (2)	0.33 (3)	0.26 (3)	0.18 (3)	0.25 (3)	0.25 (3)	0.16 (3)	0.06 (1)	0.00 (0)
Community Care											
Health Visitor	Visits	0.83 (46)	0.49 (8)	0.24 (5)	0.85 (46)	1.50 (20)	0.44 (12)	1.25 (46)	1.36 (16)	1.00 (12)	1.00 (3)
Social Worker	Visits	0.41 (14)	0.21 (3)	0.23 (4)	0.46 (10)	0.61 (14)	0.22 (3)	0.52 (10)	0.67 (5)	1.28 (14)	1.20 (2)
Physio-therapist	Visits	2.09 (40)	1.76 (40)	1.74 (12)	2.11 (16)	2.56 (20)	1.72 (40)	2.31 (16)	2.60 (15)	4.94 (20)	2.40 (4)
Psychologist	Visits	0.12 (40)	0.08 (4)	0.13 (6)	0.11 (10)	0.17 (4)	0.07 (10)	0.18 (6)	0.15 (4)	0.33 (3)	0.00 (0)
Counsellor	Visits	0.10 (7)	0.06 (4)	0.04 (2)	0.04 (3)	0.23 (7)	0.04 (3)	0.10 (4)	0.27 (7)	0.22 (2)	0.00 (0)

Table 4.5 – Direct healthcare costs by health stage and system, mean, £ sterling (95% CI)

		Kings				MiToS				
Category	Full Sample	Stage 1	Stage 2	Stage 3	Stage 4	Stage 0	Stage 1	Stage 2	Stage 3	Stage 4
Primary Care	164 (132, 196)	74 (50,92)	113 (52,173)	118 (77,154)	329 (237,424)	77 (61,87)	259 (134,384)	392 (186,598)	420 (186,652)	1054 (597,1510)
Secondary Care	1,183 (896,1502)	572 (324,639)	899 (405,1586)	927 (809,1514)	2146 (1507,2930)	642 (449,838)	1668 (1376,1781)	1724 (987,2507)	837 (243,1616)	944 (54,2546)
Of which are inpatient stays	763 (521,1037)	256 (80,281)	575 (150,1199)	523 (186,1028)	1520 (999.2186)	326 (187,489)	1115 (937,1130)	1155 (554,1802)	375 (0,937)	675 (0,2024)
Tests	110 (94,128)	133 (94,172)	129 (92,168)	115 (84,148)	85 (54,122)	575 (150,1199)	113 (81,150)	83 (32,142)	25 (16,55)	2 (1,5)
Community services	250 (222,283)	184 (120,263)	173 (114,226)	262 (211,320)	367 (303,432)	167 (141,197)	308 (254,372)	370 (279,468)	563 (316,913)	377 (262,484)
Drug costs	161 (127,201)	99 (51,188)	76 (58,97)	86 (70,105)	369 (303,432)	94 (73,127)	192 (121,283)	302 (189,441)	386 (160,687)	271 (43,580)
Total Direct Costs	1889 (1596,2214)	1096 (757,1240)	1353 (879,2002)	1534 (1111,2123)	3311 (2666,4151	1329 (532,1700)	2678 (1948,3545)	2899 (2190,3840	2281 (1613,2988)	2666 (1292,4597)

Table 4.6 - Generalized Linear Models, showing influence of disease staging, onset type, and demographic variables on total costs

Variable	Coefficient (SE)	Relative increase in costs associated with variable*	p-value
Kings Staging			
Constant	7.02 (0.53)		<0.01
Kings 2	0.36 (0.26)	1.43 (1.11, 1.86)	0.17
Kings 3	0.50 (0.25)	1.65 (1.28, 2.12)	0.05
Kings 4	1.24 (0.26)	3.45 (2.66, 4.48)	<0.01
Bulbar onset	0.07 (0.19)	1.07 (088, 1.30)	0.25
Respiratory onset	-0.67 (0.57)	0.51 (0.29, 0.90)	0.71
Gender (male = 1)	0.01 (0.16)	1.01 (0.97, 1.05)	0.98
Age (years)	0.001 (0.01)	1.001 (0.999, 1.002)	0.88
Time since diagnosis (months)	-0.01 (0.002)	0.99 (0.98, 1.0)	<0.01
MiToS Staging			
Constant	7.13 (0.45)		<0.01
MiToS 1	0.84 (0.15)	2.32 (1.99, 2.69)	<0.01
MiToS 2	0.98 (0.22)	2.66 (2.14, 3.32)	<0.01
MiToS 3	0.92 (0.41)	2.51 (1.67, 3.78)	0.07
MiToS 4	0.79 (0.75)	2.20 (1.04, 4.66)	0.29
Bulbar onset	0.32 (0.16)	1.38 (1.17, 1.62)	0.04
Respiratory onset	-0.32 (0.51)	0.73 (0.44, 1.12)	0.53
Gender (male = 1)	0.01 (0.04)	1.01 (0.97, 1.05)	0.97
Age	0.001 (0.01)	1.001 (1.0, 1.002)	0.98
Time since diagnosis (months)	-0.01 (0.002)	0.99 (0.98, 1.0)	<0.01

4.4 Discussion

This analysis of health utility and costs by clinically defined health stages provides empirical evidence of the impact of the progressive nature of MND, and data to support future economic evaluations in MND. This study benefitted from using two commonly used health staging systems, Kings and MiToS staging, and represents the most comprehensive health utility and cost study in MND.

The mean, 3-month NHS costs of £1,889 is significantly higher than estimates for some other neurodegenerative conditions (e.g. £529 for patients with Parkinson's disease [228]) and comparable to others (e.g. £1,880 for patients with Huntington's disease [229]). The comparison between our study and earlier estimates of the costs of MND in the UK is difficult because of difference in methodology and staging systems used. However, our study appears to have a higher cost for the most severe Kings state, (£3,311 over 3 months)

compared to the most severe state in Munsat et al [7] (£5,825 over 12 months), after accounting for inflation. This could be attributed to our study accounting for a wider scope of costs such as home-based care, and using resource use information from patient survey questions rather than relying on expert opinion, which is less reliable [208]. A substantial portion of costs (40%) in our study population related to hospital admissions, which occurred at a rate of 92 per 100 patient-years. This reflects the gravity of MND, and the frequent need of patients for specialist medical care.

The Kings staging system showed that patients incurred increased costs with more severe health stages: Kings stage 4 had significantly higher costs than other Kings stages, which is likely a result of this stage being defined by nutritional and respiratory failure, and survival requiring gastrostomy feeding or respiratory support such as non-invasive ventilation. Patients in Kings stages 1 to 3 also show increasing costs, which was expected as these stages reflect an increasing number of body regions affected by the condition. Higher costs in MiToS stage 1 compared to 0 may be explained by this involving the first loss of independence. MiToS stages 2 to 4 were associated was smaller marginal increased costs, as once independence has been lost in one domain, other losses may not result in increased healthcare costs, although it should be noted that the number of patients in these categories were relatively low.

The mean health utility of patients in the sample was 0.57, with individual responses across the full range of the EQ-5D-5L index. The largest health utility decrement between consecutive states was from Kings stage 1 to stage 2, indicating that losing functioning in a second domain may impact health-related quality of life more than subsequent additional losses, and suggesting a diminishing marginal negative impact on health utility with disease severity. Health utility was lower for people in more severe stages compared to less severe stages in both the Kings and MiToS systems, reflecting the higher percentages of more severe responses across the 5 domains of the EQ-5D-5L in more advanced stages. It should be noted, however, that as the data are based on a cross-sectional analysis, inferences on longitudinal effects are speculative. Bulbar onset patients in our study tended to have higher EQ-5D-5L health utility than patients with limb or respiratory onset. This result may be in part due to the domains featured in the EQ-5D-5L, which could be expected to capture losses in mobility, which is impacted more in limb onset, than symptoms that are more prominent in bulbar onset.

Health state utilities by Kings staging have been reported previously using the EQ-5D-3L [156]. Our reporting of EQ-5D-5L utilities may mitigate ceiling/floor effects, although insufficient data has been presented in previous studies to evaluate this. Health utilities reported using the EQ-5D-3L are considerably lower across all King's health states (1 to 4) when compared to our study (0.65, 0.53, 0.41 and 0.27 using EQ-5D-3L, compared to 0.71, 0.60, 0.53 and 0.50, using EQ-5D-5L). This could be attributed to the revised tariffs used in our study, but also to the easing of flooring effects. EQ-5D VAS scores showed better agreement between our study and Jones et al. [156], with the two studies having comparable values for all Kings states. This highlights the differences in structure between the EQ-5D-3L and 5L questionnaires and could provide evidence to suggest the 5 level questionnaire is more sensitive to changes in quality of life in people with MND as the disease progresses.

Differences between the Kings and MiToS staging systems in terms of patient distribution, costs and health utility can be explained by their construct [230]. In the Kings staging system, the focus is on disease spread through upper and lower limbs as well as bulbar regions. Disability in these regions is defined as any loss (any score below 4) in certain ALSFRS-R items. Stages 1, 2 and 3 are assigned by counts of these disabilities. The model also has a mechanism which assigns patients with swallowing or respiratory failure to the most severe stage 4. In contrast, the MiToS system is structured around loss of independence in domains of bulbar, gross motor, fine motor and respiratory loss. Loss of independence in these domains requires respondents to score a 0 or 1 on certain ALSFRS-R items. These scores are low as all items cover a range from 0 to 4. Patients are assigned stages based on a count of affected domains. No mechanism within the MiToS system allocates patients to the most severe stage in the MiToS model if nutritional or respiratory failure occurs.

Limitations of our study include the low number of patients in stages 3 and 4 of the MiToS staging system, and no estimates for caregiver and other indirect costs which are likely to be high [231,232]. Further to this, our study presented cross-sectional results rather than longitudinal and used episode costs for inpatient admissions as the length of hospital stay of patients was unknown.

In conclusion, while it is well understood that MND lowers patients' health-related quality of life and is associated with substantial costs to health care systems, the evidence presented

herein provides a basis for future health economic analyses of interventions for MND. Our use of two well established health staging systems, Kings and MiToS, allows for costs and utilities to be assigned to MND health states for use in health economic models.

Preface to Chapter five

The previous chapter presented health utilities and costs by a UK perspective by commonly used MND staging models, making use of the relatively large TONiC MND dataset. These are key parameters needed in any economic evaluation of new treatments. Edaravone is the first drug approved by the FDA is over 20 years for the treatment of MND and may mark the start of a range of new potential treatments emerging for MND in the not too distant future.

Chapter five uses the data generated in chapter four to carry out a cost-utility analysis of edaravone from a UK health payer perspective. It makes use of the PRO-ACT dataset to address some of the limited trail data, and uses Markov modelling to estimate the cost-effectiveness of edaravone. It highlights the influential factors and assumptions which impact on the cost-effectiveness estimates significantly and offers a narrative on future health economic considerations which may be relevant to treatments which may become available for MND. This analysis can be thought of as an early/indicative economic analysis of edaravone in a UK healthcare setting for the treatment of MND.

Chapter five

Economic evaluation of edaravone with standard care compared to standard care alone for the treatment of Motor Neurone Disease in the United Kingdom using Markov Modelling

Abstract

Background: Motor Neurone disease (MND), also known as Amyotrophic Lateral Sclerosis (ALS), is a rapidly progressive neurodegenerative condition which is associated with a substantial impact on quality of life and severely shortened life expectancy. To date, only one disease-modifying drug (riluzole) has been approved for use in the National Health Service (NHS) in the United Kingdom. Edaravone is a new treatment, approved by the Food and Drugs Agency (FDA), for MND after a clinical trial showed the drug to be effective in slowing the rate of functional decline. This clinical improvement was only shown in a small subset of people with less severe disease (as defined as having relatively high functioning as defined by the ALSFRS-R). However, edaravone is likely to be a high-cost treatment, therefore it is important to estimate the cost-effectiveness of this treatment. The aim of this study was to provide the first cost-utility analyses of edaravone in a U.K setting (NHS payer prespective) and to highlight potential health economic modelling issues for future treatments for MND. Despite the manufacturer of edaravone withdrawing its license application to the European Medicines Agency (EMA), results from this study can still be informative.

Methods: We used Markov modelling to present cost-effectiveness analyses for edaravone with standard care compared to standard care alone for treating motor neurone disease from a U.K health service payer perspective. This analysis made use of patient-level cost and utility data from the Trajectories of Outcome in Neurological Conditions (TONiC) dataset, a large U.K MND study, to estimate health state utilities and costs (£, cost year 2017) according to both the Kings ALS and MiToS staging systems. Transitions between Kings ALS states for the pivotal edaravone trial (over 6 months) were estimated from the published trial results, with transitions following this period estimated from a cohort of patients from the Pooled Resource Open-Access ALS Clinical Trials (PRO-ACT) database, matched according to the trial inclusion criteria. Results were estimated over a lifetime horizon.

Results: The base case Incremental Cost-Effectiveness Ratio (ICER) was £1,423,985 per quality-adjusted life year (QALY) gained using the Kings ALS staging system. One-way sensitivity analysis highlighted that the price of edaravone, and the administration costs of the drug, are major drivers of the ICER. The ICER also differed depending on which Kings ALS health stage the treatment was initiated and stopped, and the data source used for transition probabilities. Clinical trial evidence was a central limitation, which added uncertainty to results and required the use of several modelling assumptions. There are also issues around the strict inclusion criteria for the MCI186-19 clinical trial, as a previous trial which had a broader inclusion criterion failed to show any statistically significant improvement in ALSFRS-R scores. Therefore, cost-effectiveness results are only relevant to a small subset of less severe MND patients.

Conclusion: Under the most plausible modelled scenarios, edaravone is unlikely to be cost-effective as a treatment for people with MND at a £30,000 cost per QALY threshold which is commonly used as the upper limit of acceptability by NICE. There is considerable uncertainty surrounding the clinical benefit associated with edaravone. In spite of this, we have presented useful insights into the factors which influence the cost-effectiveness of edaravone, which may also apply to future potential treatments for MND.

5.1 Introduction

Motor Neurone Disease (MND), also known as Amyotrophic Lateral Sclerosis (ALS), is a terminal neurological condition which attacks the motor neurons in the brain and spinal cord and leads to a progressively worsening state of functioning [180]. Symptoms include reduced mobility, loss of speech ability and respiratory insufficiency. The condition is also associated with significant caregiver burden and high healthcare costs [207].

Only one disease-modifying drug (riluzole) has been approved (in 2001) by the National Institute for Health and Care Excellence (NICE) for use in MND in the National Health Service (NHS) [95]. Riluzole was shown to modestly increase survival, by between 2 to 4 months [233]. The health economic analysis underpinning the decision for NICE approval used Markov modelling, but used a health staging system [234] which has been replaced by other more accepted models of disease progression [235,236]. A recent study indicated that most of the survival benefit of riluzole is seen at more severe stages of the disease, based on a more accepted model of disease progression [237].

More recently edaravone, a free radical scavenger, has been shown to slow down progression of MND based on ALSFRS-R index and item scores within a small subgroup of less severe patients [238]. The exact mechanism of action by which edaravone provides therapeutic effect in MND is unknown but tt is believed to prevent oxidative stress damage to motor neurones [239]. ALSFRS-R is a validated, disease-specific measure of functionality and is the most used efficacy outcome measure in MND trials [240]. In an initial phase 3 trial, edaravone did not shown any significant difference in ALSFRS-R decline between the intervention and placebo when based on the intention-to-treat population (−5.70 ± 0.85 in the edaravone groups compared to −6.35 ± 0.84 in the placebo group, p value = 0.411) [241]. A *post hoc* analysis of patients with less advanced MND found that there was a significantly positive result in favour of edaravone in terms of ALSFRS-R decline [242]. This led to a further confirmatory trial using stricter inclusion criteria matching the group in which the drug showed efficacy. This confirmatory trial (MCI186-19) showed that edaravone showed a positive and statistically significant difference in ALSFRS-R decline over 6 months (5·01 (SE 0·64) in the edavarone group and -7·50 (0·66) in the placebo group, p value = 0.0013) [238]. The strict criteria for inclusion has led to issues of generalisability of the results to the wider MND population, with one study estimating that only 7% of those on MND registers would meet the criteria for inclusion in the pivotal edaravone trial (MCI186-19) [243].

However, the Food and Drug Agency (FDA) has approved edaravone for use in the US in all MND populations, regardless of severity. In this analysis, we present cost-effectiveness results for edaravone for people with MND from a U.K healthcare payer perspective.

5.1.1 Edaravone withdrawal of license application to the European Medicines Agency

The manufacturer of edaravone has currently withdrawn their application to the European Medicines Agency (EMA) at the time of writing. The EMA cited several issues with the application, including short trial duration, lack of comparative survival data and the restrictive inclusion criteria [244]. The EMA also cited concerns surrounding the rationale behind the proposed dosing schedule and an uncertain mechanism of action of edaravone in MND patients. In spite of this, we consider that an economic evaluation of edaravone would be a valuable addition to the literature as it can give important insights into challenges of decision-making in this disease area, in particular; highlighting key parameters and assumptions and their impact on the cost-effectiveness estimate. The aim of this study is to provide an early/indicative economic analysis to estimate the cost-effectiveness of edaravone on the available evidence. It also attempts to highlight the type of evidence that would assist future health economic evaluation of treatments for MND. In 2019, the Canadian Agency for Drugs and Technologies in Health (CADTH) reported cost-effectiveness analysis of edaravone for treatment of MND from a Canadian health system perspective [245]. Our analysis has some key differences and reports for a UK health payer perspective.

5.2 Methods

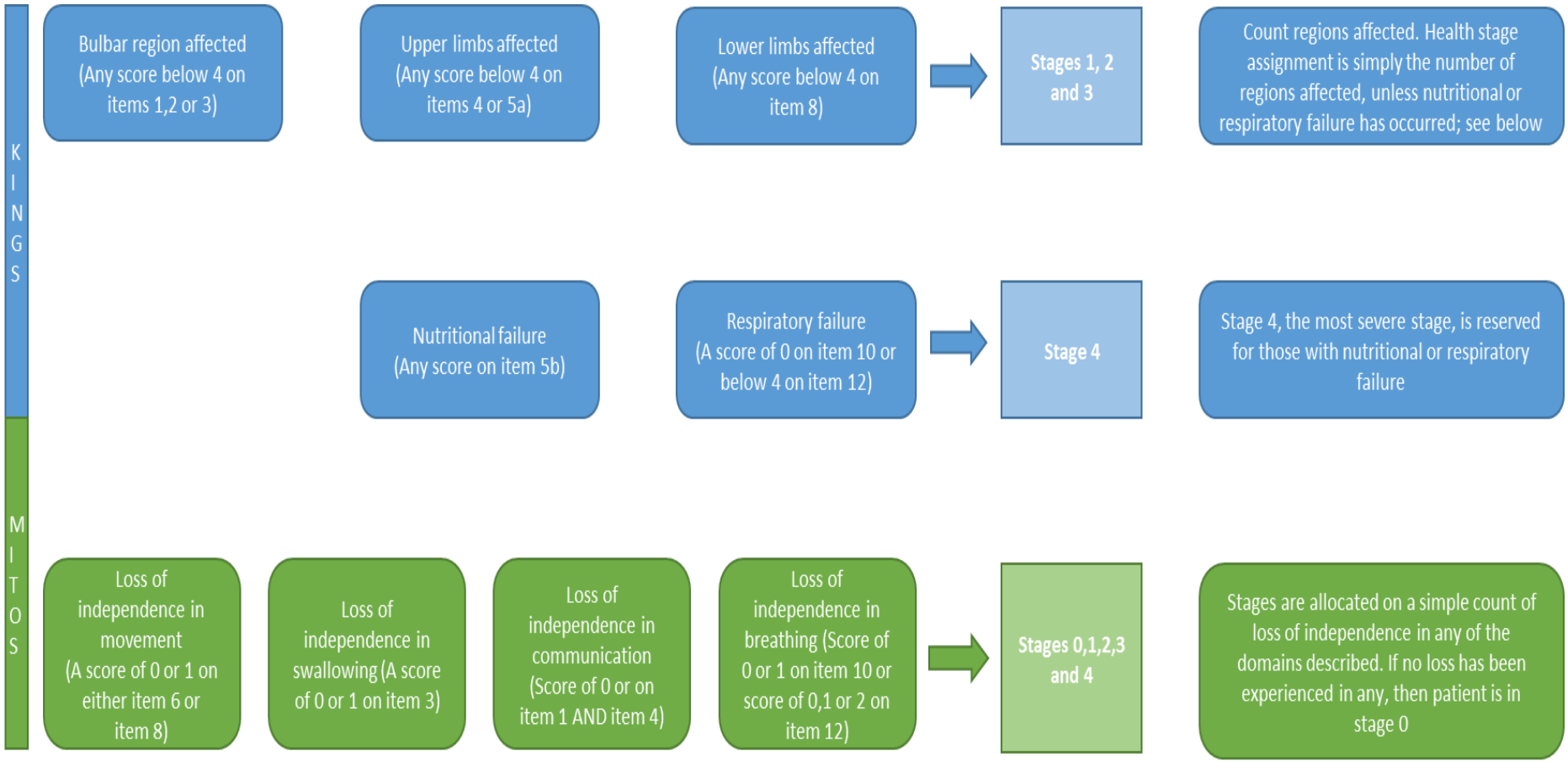
Methods described in this section follow those recommended in the Consolidated Health Economic Evaluation Reporting Standards (CHEERs) checklist [246]. We used Markov modelling to estimate the cost-effectiveness of edaravone with standard care compared to standard care alone. In this context, standard care may consist of riluzole and multi-disciplinary care such as physiotherapy, nutritional and speech therapy. It is assumed that edaravone is given in addition to standard care, to match the clinical trial. Markov models are particularly suited for economic analyses in chronic diseases that can be represented by discrete health states [247]. Markov models also allow short trial evidence, such as that generated from the edaravone trial, to be extrapolated over a longer time period. Patients are assigned to mutually exclusive health sates, and transition among these health states over

time (during cycles) in both the intervention and control group. Costs and health utilities are assigned to each health state. Markov models require data on costs, health utilities, transition probabilities and a health state system. Data informing this analysis comes from the pivotal edaravone trial, which showed a statistical difference in ALSFRS-R decline compared to placebo, and from the Pooled Resource Open-Access ALS Clinical Trials (PRO-ACT) dataset [248]. Details of how these sources are used is outlined in the sections below.

5.2.1 Health staging systems

We used the Kings ALS Staging system to describe clinically and economically meaningful health states over the course of the disease in our base case analysis [235]. Kings ALS Staging is based on the number of body regions affected and is clinically defined by physicians. It is possible to map from the commonly used MND specific measure ALSFRS-R with good precision using an algorithm based on relevant ALSFRS-R items which correspondent to functioning according to the Kings ALS staging [249]. Kings ALS staging is the most commonly used staging system. In sensitivity analysis we report results using the MiToS staging system, which focuses on loss of independence in various domains [236]. A recent study concluded that although the two systems define progression quite differently, they can be used to complement each other in analyses [249,250]. Figure 5.1 shows an overview of both systems. Analysis was carried out using Microsoft Excel.

Figure 5.1 – Shows the models used for base case analysis and sensitivity analysis along with details on how to stage patients based on ALSFRS-R items. The Kings staging system was used for base case analysis, and MiToS staging was used in sensitivity analyses



5.2.2 Health state utility

Health utility data have been reported by Kings and MiToS health stages using cross-sectional patient level data from the Trajectories of Outcome in Neurological Conditions (TONiC-MND) study in the UK [251], and these are used in this chapter. EQ-5D-5L utility values are used in the base case, as these come directly from this analysis [251]. The study also reported preference-based utility values for a UK population, which is considered appropriate.

5.2.3 Cost data

Cost data has been reported in analyses of both the Kings and MiToS health staging systems using patient data from the same TONiC study in chapter 4 [251], which included costs of current MND care in the U.K, such as drug costs (i.e riluzole), multidisciplinary care, hospital costs, primary and secondary care costs and social services costs. This was used for health state costs in the analysis. In the standard care cost model arm, only health state costs were included, whereas edaravone drug and administration costs were included in the edaravone arm in addition to health state costs, as edaravone is assumed to be given in addition to standard care. No data or evidence were available to inform whether edaravone reduces health state costs compared to standard care. Intervention costs of edaravone were informed by the clinical information regarding the administration of the drug, which involves patients having infusions of the drug for one hour every day for 14 days followed by a 14-day break in the first month cycle [252]. Each subsequent treatment cycle involved 10 days of one-hour infusions over a 14-day period followed by a 14-day break. We used NHS reference costs [253] for chemotherapy infusion, which we assumed to be similar in nature to the proposed infusions of edaravone and are likely to be comparable. The potential price of edaravone in the U.K is unknown. We used the U.S list price in our base case analysis, converted to British pounds (£).

Costs and benefits were discounted at the NICE recommended levels of 3.5% per year in our base case analysis (see table 5.3 for list of costs used) [254].

5.2.4 Population matching using PRO-ACT

To stage patients by health staging systems, ALSFRS-R item score data is needed. Baseline (or final) ALSFRS-R item scores were not reported in the pivotal edaravone trial and despite a request for these data sent to the authors of the study, these were not provided. Therefore we estimated baseline values for each ALSFRS-R item by using some of the key inclusion criteria of the trial applied to the PRO-ACT database, which is a large dataset of patient-level data from failed MND trials [248]. Matching using the PRO-ACT database was based on time since disease onset (< 2 years), ALSFRS-R items 1-9 equal to a score of 2 or more with respiratory ALSFRS-R items (10-12) equal to scores of 4 (no functional loss) and no gastrostomy required, This resulted in a final cohort of 250, which were staged according to the Kings staging system (see tables 1 and 2).

Table 5.1 - Edaravone clinical trial MCI186-19 Inclusion and exclusion criteria

Inclusion criterion for edaravone trial MCI186-19	PRO ACT Data matching
Onset of MND within 2 years	Yes
4 points (Full Score) on ALSFRS-R items 10,11 and 12 (Dyspnea, Orthopnea and Respiratory insufficiency)	Yes
% Functional Vital Capacity = 80% or more	No
ALSFRS-R score to have changed by -1 to -4 over a 12-week pre-observation period	No
All ALSFRS-R items to have a score = 2 or more	Yes
Japanese ALS Severity Scale Grade 1 or 2	No
El Escorial revised Airlie House diagnostic House Criteria = Definite or Probable	No
Without the need for gastrostomy	Yes

Table 5.2 – Baseline characteristics of PRO-ACT patient cohort

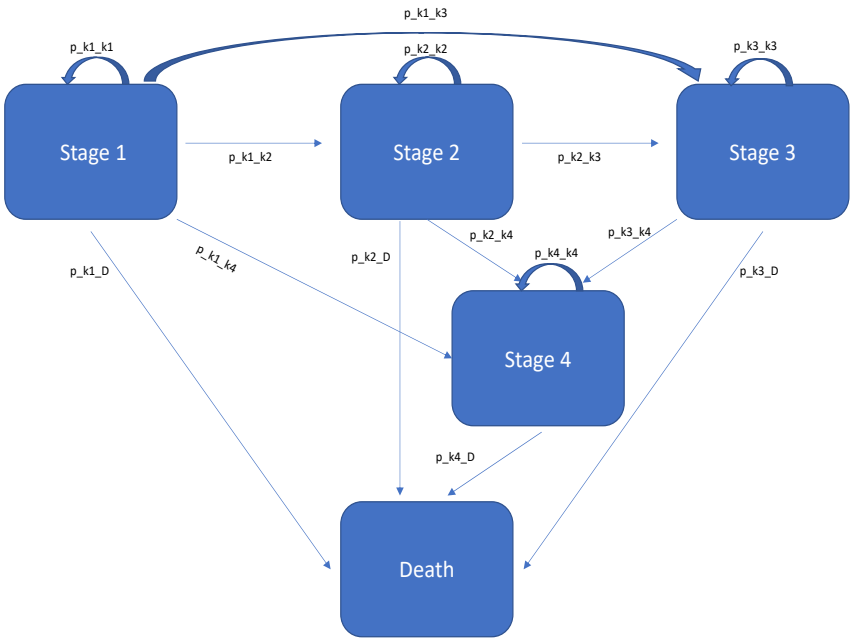
Characteristics (mean, range)	Matched PRO-ACT cohort n=250	Edaravone trial population (MCI186-19) n=137
Time since disease onset months (SD)	19.7 (3.4)	18.1 (3.7)
ALSFRS-R index score	41.2 (5.6)	42.0 (5.9)
(SD)		
Age	54.7 (8.9)	52.8 (8.2)
(SD)		
% female	41.2%	44.4%

SD = Standard deviation

5.2.5 Transition probabilities and cycle length

Transitions between health states for the Kings ALS staging system was estimated based on the published data from the edaravone trial, which described mean changes in each ALSFRS-R item from baseline and 6 months, along with the associated standard deviation [238]. Patients can start in the model in either Kings stage 1, 2 or 3. Patients may remain in the stage they were in at the start of the cycle, or transitions can occur between any stage and any more severe stages or death. To reflect the progressive degenerative nature of MND, no transitions were permitted to less severe stages. The model structure highlighting transitions through the Kings staging can be seen in figure 5.2.

Figure 5.2 model structure with possible Kings staging transitions



The change in ALSFRS-R items over 6 months in the MCI186-19 trial [238], was applied to the matched PRO-ACT cohort ALSFRS-R scores to estimate the transition probabilities of patients receiving edaravone with standard care and standard care alone. This was accomplished by assuming changes in ALSFRS-R item scores to be normally distributed, and using Monte Carlo simulation to sample from distributions corresponding to each item, to estimate the change in ALSFRS-R item scores for each matched PRO-ACT patient. As ALSFRS-R item scores are discrete values, we rounded simulations in order to allocate a

Kings stage. and tested each of the resulting transitions for face validity (as compared to transitions previously published using Kings staging) for use in our base-case analysis. The rounded-up analysis provided the most plausible transitions and therefore was selected for use in the base case analysis, except for the transitions from Kings stage 4 to death. Therefore, in the base case we use the transitions from stage 4 to death from a previously published PRO-ACT study [255]. The rationale for using a different source for the transition from stage 4 to death was that once a patient had reached stage 4 (need for tractotomy or gastrostomy), the transition probability should not depend on prior transitions.

Cycle length was defined as 3 months, which was based on the low life expectancy of the cohort and the fact that our cost and health utility data was also based on a 3-month period. A half cycle correction was also undertaken, and a lifetime time horizon used. The incremental cost-effectiveness ratio (ICER) was calculated using the average time spent in each health stage, estimated over the lifetime of the model, with the relevant costs and quality-adjusted life years (QALYs) being attributed to the time in each health stage. This was done for both the edaravone with standard care and standard care alone arms, which resulted in incremental costs and QALYs estimates.

5.2.6 Key assumptions used

As long-term data is limited, certain assumptions are made in the analysis. A key assumption in our analysis was that edaravone would only be effective in early Kings stages (stages 1 and 2). This was based on published data which showed that ALSFRS-R decline was not statistically significant between edaravone and placebo in more severe MND populations [241,256]. Other assumptions are based on observed data also. No deaths were observed in the edaravone trial, nor were there any patients who transitioned to Kings ALS stage 4 (nutritional or respiratory failure). Further to this, no transitions from Kings stage 3 to other stages were observed in the pivotal edaravone trial. In the model used in our study, no transitions to Kings stage 4 or death occur until cycle 3 (6-9 months). Transitions to Kings stage 4 from other stages and from all stages to death were estimated from the same matched PRO-ACT population and observing transitions from month 6 to 12 in this dataset. These transitions are assumed to hold in the model from cycle 3 onwards.

5.2.7 Sensitivity analyses

To describe the level of uncertainty surrounding results, we undertook several one-way and two-way sensitivity analyses to account for parameter uncertainty and to establish influential factors on the ICER. In these analyses we assumed various reductions in the costs of the drug edaravone and the costs associated with its administration. Further to this, an analysis in which all health state costs are doubled is presented. We also provide results using the ED-5D-3L utility values from the literature for Kings ALS staging [257] and ALS utility index (ALSUI) which is an MND disease specific preference-based measure [258].

5.2.8 Scenario analysis

In addition, we carried out scenario analysis; to test the impact of various assumptions on the cost-effectiveness results. These analyses varied the time (defined by specific health states) at which edaravone is initiated and stopped. There is currently no clear guidance on when edaravone treatment should be stopped, short of stopping due to adverse events. Limited published evidence from the US suggests that treatment with edaravone is not continued to death, with reasons for discontinuation including disease progression amongst others [259]. Another analysis assumed that edaravone is stopped at 6 months, the same duration of the edaravone trial data used.

We present results for a scenario in which the original stage 4 to death transitions from the PRO-ACT dataset are used, as opposed to the base case which uses published stage 4 to death transitions [255]. We also display results using a different source of transition probabilities based on the full PRO-ACT dataset (A more general MND population – as used in the CADTH analysis) [245]. Further to this, we also report results using the MiToS staging model as an alternative to the base-case model of Kings ALS staging [236]. It was not possible to estimate transitions in the MiToS model analysis using the methods outlined in section 2.5. Instead we applied a constant hazard rate of 0.66 (relative difference in ALSFRS-R decline in edaravone trial and the rate used by CADHT) to MiToS transitions from stage 0 to 1, at which point we assumed treatment would stop.

Table 5.3 – Health state costs, utilities and intervention costs

Model/ Stage	Health Utility (95% C.I)	Health Stage Costs (£) (95% C.I)		Intervention Cost Items (edaravone) in Kings stages 1 and 2 and MiToS stage 0		Source
Kings						
Stage 1	0.76 (0.71,0.80)	1096 (757,1240)		Drug Costs (1st cycle)	£30,336	U.S list price = $145,000 per year
Stage 2	0.60 (0.56,0.64)	1353 (879,2002)		Drug Costs (subsequent cycles)	£26,767	
Stage 3	0.53 (0.50,0.56)	1534 (1111,2123)		Administration costs (1st cycle)	£7,697	NHS reference costs – SB152
Stage 4	0.50 (0.45,0.54)	3311 (2666,4151)		Administration costs (subsequent cycle)	£6,997	
MiToS						
Stage 0	0.71 (0.69,0.73)	1329 (532,1700)				
Stage 1	0.48 (0.44,0.51)	2678 (1948,3545)				
Stage 2	0.36 (0.31,0.42)	2899 (2190,3840				
Stage 3	0.33 (0.23,0.43)	2281 (1613,2988)				
Stage 4	0.25 (0.07,0.42)	2666 (1292,4597)				

Table 5.4 - Summary of economic model and evidence base

Parameter	Description of analyses/rationale
Model type	Markov model. This type of model is well suited to chronic and progressive diseases (such as MND).
Model Structure	In the base case, the Kings ALS staging model is used. The Kings model is the most used model in MND and has been shown to not be associated with backward transitions [235]. In addition, the clinical trial included MND patients with early disease stages and relatively high functioning, and the Kings staging system has been shown to provide higher resolution of progression in early MND stages [19]. The MiToS staging system is also commonly used and a scenario analysis using this system is provided, but results are more uncertain due to the nature of the trial evidence.
Population	Those eligible for enrolment in the MCI186-19 clinical trial of edaravone compared to placebo [238]. This included a restricted population and enrolled only people with: • Time since disease onset of <2 years, and

	• ALSFRS-R items 1-9 equal to a score of 2 or more and • Respiratory ALSFRS-R items (10-12) equal to scores of 4 (no functional loss), and • No gastrostomy required The cost-effectiveness results therefore are only generalisable to this MND population. The size of the potential eligible population in the U.K for edaravone if approved is uncertain and would be linked to any NICE recommendation, but based on a study which stated only 7% of MND patients would meet the inclusion criterion of the clinical trial, and a MND prevalent population of 4,000 – 5,000 [35] means 280 – 350 may be eligible, but it should be noted these numbers would increase when people with newly diagnosed MND are considered for treatment.
Intervention and place in pathway	Edaravone. Assumed to be given in addition to standard care (comparator). Therefore, edaravone is positioned as a first-line treatment for people with earlier stages of MND.
Comparator	Standard care. This includes riluzole, multidisciplinary care hospital care, primary and secondary care and social services.
Outcomes	The primary outcomes in the model are quality-adjusted life years which are calculated by estimating transitions between health states over time. The time spent in each health stage is associated with health state utility. Treatments which allow longer time to be spent in less severe states generate higher utility and QALY estimates. Carer quality of life and adverse event rates were not able to be estimated due to a lack of data.
Study perspective	Costs and outcomes linked to an NHS perspective, as in NICE reference case. An assumed willingness to pay threshold of £20,000 to £30,000 per QALY gained is used as based on the NICE reference case.
Cohort size Time horizon and cycle length	A hypothetical cohort of 1,000 MND patients started in the model. A 15-year time horizon was used, at which point all patients in the model had transitioned to the death state. A cycle length of 3 months was selected to capture the fast progressive nature of MND and to align with cost data, which was collected over a 3-month period.
Costs and health state utilities	Costs and health state utilities for both Kings and MiToS staging systems are used from the chapter 4 study [251], which reported these outcomes from a U.K MND population. Cost year 2017, reported in pounds sterling (£).
Patient data (PRO-ACT data matching)	The PRO-ACT dataset was used to generate a dataset with patients who matched the inclusion criterion from the MCI186-19 clinical trial. PRO-ACT is an open-source resource and contains data for MND patients enrolled in MND trials in which intervention treatments had not shown to have any clinical benefit. This data includes ALSFRS-R item scores and

	time since disease onset. The data matching was done by applying criterion as outlined in table 5.1, which resulted in a sample size of 250 patients. This informed the baseline ALSFRS-R scores and clinical stage.
Efficacy data	Efficacy data comes from the MCI186-19 clinical trial [238], which reported changes in each ALSFRS-R item over a 6-month trial period.
Model transitions	Model transitions were estimated by applying ALSFRS-R item changes from the MCI186-19 trial data to the baseline ALSFRS-R of the matched PRO-ACT dataset. Transitions were estimated for each 3-month cycle between each health state. 3-month health state transitions beyond the 6 month trial data was estimated by allowing transitions to Kings stage 4 and death, informed by longer term transitions from the PRO-Act dataset. Transition matrices can be seen in table 5.5
Model assumptions used	Several assumptions were used: • No backward transitions were permitted to reflect progressive nature of condition • No transitions to death or Kings stage 4 modelled in the 1st 6 months to reflect trial results for both edaravone and standard care arms. • Edaravone treatment only given in Kings stages 1,2 as no transitions were observed in the trial from stage 3 or stage 4 to other stages. • Transitions from Kings stage 4 to death are the same for edaravone and standard care arms based on the lack of data and the fact that prior treatments are unlikely to influence mortality rates once stage 4 has been reached. • Health stage resource use for standard care would be the same for both arms (due to lack of data). Sensitivity analyses were undertaken to test the influence of all key modelling assumptions made on the cost-effectiveness results.
Limitations of analyses	The analyses are limited by the short duration of the MCI186-19 clinical trial and lack of reported transitions between health state, which had to be estimated from a matched PRO-ACT dataset and simulated trial data. Patient-level data was also not available. In spite of these limitations, the results from the model appear to have face validity for example: • the baseline distribution by Kings staging were similar to those reported in the trial using the matched PRO-ACT approach • the survival outcomes in terms of life years and QALYs gained in the standard care model arm are reasonably aligned to life expectancy in MND in general.

5.3 Results

5.3.1 Base case

Using our matched PRO-ACT cohort data, the distribution at base line was 39% in Kings stage 1, 42.4% in Kings stage 2 and 18.6% at Kings stage 3 at baseline. This was not too dissimilar to the actual baseline stages from the pivotal edaravone trial reported in the CADHT report (39.4%, 46% and 14.4% respectively) [245]. A range of results for the base case and sensitivity analysis can be seen in table 5. Transition matrices can be seen in table 5.5.

In the base case analysis, the modelled edaravone group had on average 1.829 QALYs per person compared to 1.664 QALYs in the standard care group. The average total costs per person were £260,730 for the edaravone group and £23,841 for people receiving standard care. This results in an ICER estimate of £1,423,985 per QALY gained for edaravone with standard care compared to standard care alone. In the base case analysis, 74.6% of intervention costs came from edaravone drug costs while 24.4% of costs were associated with administration of the drug. 27.3% of incremental costs came from increased time spent in Kings stage 1, with 73.4% associated with increased time in Kings stage 2. 52.3% of incremental QALYs were accrued in extra time in Kings stage 1.

A full list of sensitivity and scenario analyses results are described below. In every analysis in our sensitivity and scenario analyses (see table 5.5), edaravone could not be considered cost-effective at the £30,000 per QALY willingness-to-pay threshold commonly used by NICE.

5.3.2 Sensitivity analysis

Sensitivity analysis showed that the cost of edaravone was a major driver of the ICER estimate. Administration costs also contributed significantly to the high ICER estimates, which is understandable given that treatment is given intravenously between 10 and 14 days per month. If the high administration costs are set to zero in the model, the ICER estimate is £1,129,683 per QALY gained. Even with a 95% discount on the US list price and zero administration costs the ICER is estimated to be £55,132 per QALY gained. Setting edaravone drug cost to zero and keeping full administration costs were still associated with an ICER of £292,752 per QALY gained. Doubling Kings health state costs did not have a major impact on the ICER. One-way sensitivity analysis was also used to investigate the

impact of varying the source used for utility values in the model. Using published Kings EQ-5D-3L utilities (as opposed to the EQ-5D-5L values in the base case), the ICER increases slightly from £1,423,985 to £1,497,834 per QALY gained. Similarly using ALS utility index values from our previous analysis changed the ICER to £1,491,796 per QALY gained.

5.3.3 Scenario analysis

Using the original matched PRO-ACT cohort transition for stage 4 to death transition resulted in an ICER estimate of £1,331,448 (£237,097 incremental costs and 0.178 incremental QALYs). The use of the published PRO-ACT transitions, which includes a broader MND population (rather than the edaravone trial inclusion matched PRO-ACT population used in the base case,) and applying a hazard ratio of 0.66 (as used by the CADHT study) reduced the base case ICER to £823,500 per QALY gained. The use of the rounded analysis to estimate transition probabilities from the trial data (see methods section 2.5) in place of the base case rounded up analysis, did not impact the ICER estimate significantly.

Scenario analyses showed that the ICER was sensitive to treatment starting and stopping rules, defined by Kings health stage. In our base case analysis, we assume that edaravone treatment can be given in either stage 1 or 2 and stopped when patients progress to stage 3 or later. When edaravone is started in stage 1 and stopped in stage 2 the ICER reduces from £1,423,985 to £876,897 per QALY gained and when stopped in stage 3 the ICER is £1,194,768 per QALY gained. When started in stage 2 and stopped in stage 3 the ICER increases to £1,766,190 per QALY gained. Another scenario analysis, in which all edaravone treatment is stopped at 6 months (the same length of comparative trial evidence), reduced the base case ICER from £1,423,985 to £1,090,565 per QALY gained.

The ICER associated with using the MiToS staging system (as opposed to the Kings ALS staging system in the base case) was £599,032 per QALY gained (£179,327 incremental costs and 0.299 incremental QALYs). It is likely that assuming that edaravone is associated the same HR of 0.66 (as this analysis did) as was used by CADTH for the Kings staging system overestimates the effectiveness of edaravone under a MiToS system. We did not have any relevant information on which to base the edaravone hazard rate for the MiToS analysis.

Table 5.5 – Three Monthly Transition probabilities for Kings and MiToS staging systems based on edaravone clinical trial and PRO-ACT database

Edaravone with standard care	1st 2 cycles				
Kings					
From/To	Stage 1	Stage 2	Stage 3	Stage 4	Death
Stage 1	0.7615	0.2049	0.0536	0	0
Stage 2	0	0.9045	0.0955	0	0
Stage 3	0	0	0	0	0
Stage 4	0	0	0	0	0
Standard care	1st 2 cycles				
Kings					
From/To	Stage 1	Stage 2	Stage 3	Stage 4	Death
Stage 1	0.6560	0.2603	0.0837	0	0
Stage 2	0	0.8226	0.1774	0	0
Stage 3	0	0	0	0	0
Stage 4	0	0	0	0	0
Edaravone with standard care	Subsequent cycles				
Kings					
From/To	Stage 1	Stage 2	Stage 3	Stage 4	Death
Stage 1	0.7279	0.1746	0.0290	0.0572	0.0115
Stage 2	0	0.8151	0.0741	0.0727	0.0381
Stage 3	0	0	0.7407	0.2254	0.0339
Stage 4	0	0	0	0.6771	0.3229
Standard care	Subsequent cycles				
Kings					
From/To	Stage 1	Stage 2	Stage 3	Stage 4	Death
Stage 1	0.6615	0.1878	0.0720	0.0572	0.0115
Stage 2	0	0.7530	0.1362	0.0727	0.0381
Stage 3	0	0	0.7407	0.2254	0.0339
Stage 4	0	0	0	0.6771	0.3229

5.3.4 Probabilistic sensitivity analyses (PSA)

Probabilistic sensitivity analyses ICER results were similar to the deterministic base case results, with the ICER reducing slightly from £1,423,985 per QALY gained to £1,372,541 per QALY gained (0.172 incremental QALYs and £236,611 incremental costs). The PSA was carried out using 5,000 runs of the model with underlying distributions applied to transition rates, utility values, and health state costs. Costs did not vary significantly in the PSA as only health state costs were varied (edaravone and administration costs are assumed

fixed). QALY gained varied more in the PSA, showing that more robust data on edaravone QALY gains would reduce the uncertainty around the ICERs, but all runs of the PSA showed substantially high ICER estimates at edaravone list price in the base case.

Figure 5.3 – Cost-effectiveness plane (PSA)

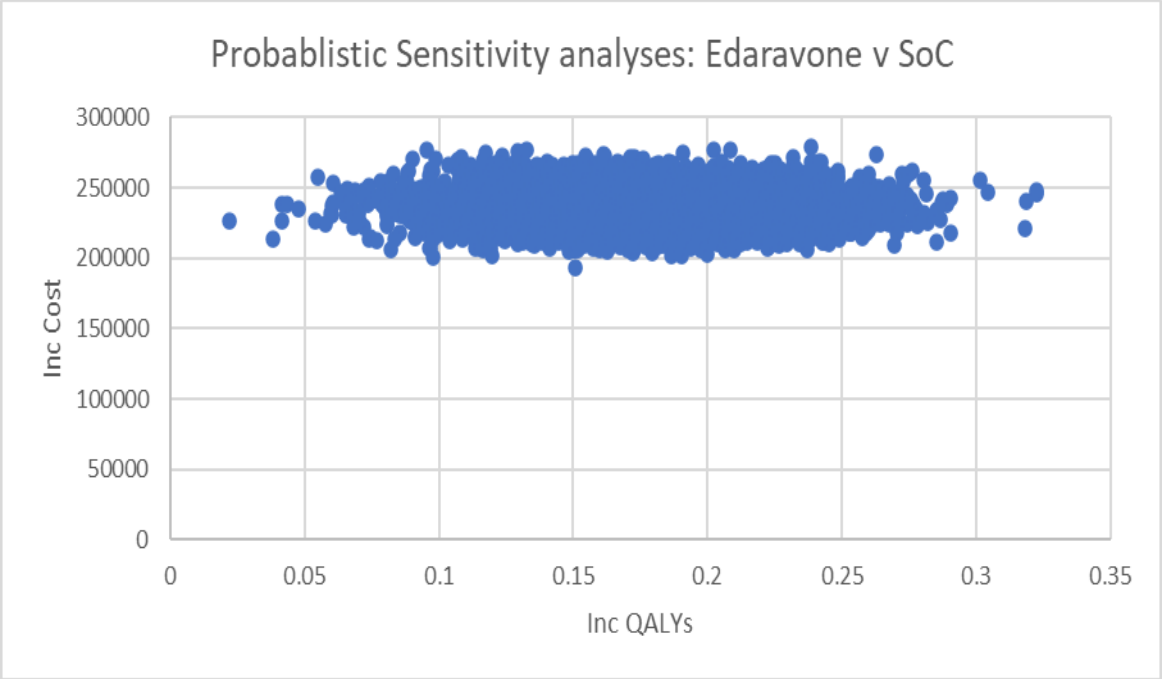


Table 5.5 - Cost-effectiveness results: Edaravone versus standard care

Scenario	Costs SoC (£)	cost edaravone	inc costs	QALYs SoC	QALYs Edaravone	Inc QALYs	ICER per QALY (£)
Base case	23,840	260,730	236,889	1.664	1.830	0.166	**1,423,984**
and 50% reduction in admin costs	23,840	240,314	216,474	1.664	1.830	0.166	**1,301,264**
no administration costs	23,840	211,770	187,930	1.664	1.830	0.166	**1,129,682**
50% reduction in price	23,840	166,636	142,795	1.664	1.830	0.166	**858,368**
95% reduction in price	23,840	81,951	58,110	1.664	1.830	0.166	**349,313**
95% reduction in price and no administration costs	23,840	32,992	9,151	1.664	1.830	0.166	**55,011**
£0 drug costs and 100% administration costs	23,840	72,541	48,701	1.664	1.830	0.166	**292,752**
health stage costs doubled	46,957	284,351	237,394	1.664	1.830	0.166	**1,427,018**
EQ-5D-3L utility values	23,840	260,730	236,889	1.412	1.573	0.161	**1,472,825**
ALSUI utility values	23,840	260,730	236,889	1.257	1.418	0.161	**1,466,889**
Treatment started in stage 1 and stopped in stage 2	19,672	153,551	133,878	1.567	1.720	0.153	**876,897**
95% reduction in price	19,672	52,498	32,826	1.567	1.720	0.153	**215,009**
95% reduction in price and no administration costs	19.672	24,926	5,253	1.567	1.720	0.153	**34,413**
Treatment started in stage 1 and stopped in stage 3	23,579	287,436	263,857	1.787	2.008	0.221	**119,476**
95% reduction in price	23,579	88,341	64,762	1.787	2.008	0.221	**293,248**
95% reduction in price and no administration costs	23,579	33,792	10,212	1.787	2.008	0.221	**46,244**
Treatment started in stage 2 and stopped in stage 3	24,082	236,078	211,995	1.550	1.670	0.120	**1,766,190**
95% reduction in price	24,082	76,052	51,970	1.550	1.670	0.120	**432,981**
95% reduction in price and no administration costs	24,082	32,253	8,171	1.550	1.670	0.120	**68,082**

Treatment stopped at 6 months	23,840	93,320	69,480	1.664	1.728	0.064	**1,090,555**
95% reduction in price	23,840	40,745	16,905	1.664	1.728	0.064	**265,354**
95% reduction in price and no administration costs	23,840	26,513	2,673	1.664	1.728	0.064	**41,945**
Base case with rounded instead of rounded up analysis	24,102	191,331	167,227	1.528	1.664	0.116	**1,434,042**
base case with PRO-ACT stage 4 transitions	**Costs SoC**	**cost edaravone**	**inc costs**	**QALYs SoC**	**QALYs Edaravone**	**Inc QALYs**	**ICER per QALY**
Treatment started in stage 1 or 2 and stopped in 3/4	19,922	257,019	237,097	1.443	1.621	0.178	**1,331,448**
and 50% reduction in administration costs	19,922	234,541	214,618	1.443	1.621	0.178	**1,205,217**
50% reduction in price	19,922	162,925	143,003	1.443	1.621	0.178	**803,051**
95% reduction in price	19,922	78,241	58,318	1.443	1.621	0.178	**327,494**
95% reduction in price and no administration costs	19,922	29,282	9,359	1.443	1.621	0.178	**52,558**
Treatment started in stage 1 and stopped in stage 2	19,922	153,395	133,472	1.787	1.936	0.149	**894,382**
Treatment started in stage 1 and stopped in stage 3	19,922	279,720	259,797	1.567	1.799	0.232	**1,121,003**
Treatment started in stage 2 and stopped in stage 3	20,154	240,067	219,913	1.328	1.461	0.133	**1,649,850**
CADHT transitions HR 0.66	Costs SoC	cost edaravone	inc costs	QALYs SoC	QALYs Edaravone	Inc QALYs	**ICER per QALY**
Treatment started in stage 1 or 2 and stopped in 3/4	23,759	216,519	192,759	1.595	1.829	0.234	**823,499**
Same HR in each stage	23,723	197,803	174,079	1.558	1.773	0.215	**808,905**
Treatment started in stage 1 and stopped in stage 2	23,558	150,108	126,549	1.702	1.879	0.177	**715,935**
Treatment started in stage 1 and stopped in stage 3	23,558	243,540	219,982	1.702	2.006	0.303	**725,118**
Treatment started in stage 2 and stopped in stage 3	23,944	191,576	167,631	1.496	1.666	0.170	**985,462**

MiToS transitions HR 0.66	Costs SoC	cost edaravone	inc costs	QALYs SoC	QALYs Edaravone	Inc QALYs	ICER per QALY
Treatment started in stage 0 or and stopped in 1/2/3/4	23,758	203,082	179,324	1.212	1.511	0.299	**599,032**
ALS Utility Index utility values	23,758	203,082	179,324	0.781	1.019	0.238	**752,227**
no administration costs	23,758	166,228	142,469	1.212	1.511	0.299	**475,920**
no administration costs and 50% discount	23,758	95,287	71,529	1.212	1.511	0.299	**238,944**

5.4 Discussion

To our knowledge, this is the first health economic evaluation of edaravone for treating MND from a UK health payer perspective. The results show that the cost of edaravone is a major influence on the ICER. However, administration costs were also considerable due to the intensive dosing regimen and means that it is unlikely that edaravone is cost-effective even at a very low price. Drug and administration costs of edaravone were added to the edaravone arm and these were the only difference in costs between the model groups. Health state costs, from standard care treatments, were assumed to be the same for each model arm, as there is no data in terms of edaravone's impact on potentially reducing standard care costs, through higher functioning for example. However, even if edaravone was assumed to reduce standard care costs, this would have very limited impact on cost-effectiveness results as these costs only accounted for a small percentage of the edaravone model arm costs. Future potential drugs for MND are likely to be expensive, due to MND being relatively rare. If they require an intensive administration regimen like edaravone, the incremental costs compared to current standard of care (riluzole – an oral treatment) will be substantially high.

This study highlights the challenges of presenting health economic analyses for potential MND treatments. The strict inclusion criteria for the edaravone trial limited the study to a small subgroup of people with MND. This inevitably questions the generalisability of the pivotal edaravone study and in what situations edaravone should be prescribed. An earlier triala have shown no significant difference in ALSFRS-R decline between edaravone and placebo groups when a broader MND population was observed [241]. Further to this, an observation study [256] has shown no significant survival difference between people with MND taking edaravone and those not when considering a broad MND population (the FDA approval for did not place any restrictions on edaravone for treating MND). Furthermore, there is no clear evidence on how edaravone impacts on survival in people with MND. In our modelling, the increase in survival and health-related quality of life in the edaravone arm stems from patients remaining in less severe states longer and transitioning to more severe states slower. This is based on edaravone being given in less severe Kings stages (stages 1 and 2). Our analysis has shown that the ICER estimate is sensitive to which Kings stages treatment is started and stopped in. If edaravone, or another treatment, is not stopped immediately after progression to a defined health stage, the cost-effectiveness results reported here would likely worsen for each scenario presented.

The short duration of the edaravone trial (6 months) raises the issue of whether the treatment is clinically effective over a longer time period. There was also no significant difference in respiratory function (ALSFRS-R items 10-12) in the trial and no patients experienced the need for tracheostomy or ventilation. Respiratory failure is the main cause of death in MND [260]. Long-term adverse event data is also lacking. Further to this, the placebo arm in the clinical trial could be considered to decline faster than expected, based on other observed studies [249]. The clinical trials were carried out in Japan, which also poses questions as to how generalizable the results are to a U.K setting. Before enrolment in the edaravone study, patients were required to demonstrate an ALSFRS-R decline of between -1 and -4 over a 3-month observation period. Therefore, no information was generated for those with slow progressing disease which did not result in a decline over the 3-month period. With all the above points considered, there is a high uncertainty regarding the clinical benefits of edaravone.

The ICER is also sensitive to the source and, perhaps more importantly, the assumptions used for transitions and treatment effect over time, therefore rationale should be given to the source and assumptions used. We consider our transition probabilities to be more representative of the population in the edaravone trial compared to an unmatched population, however each source will still have considerable uncertainties. Our cohort was limited in number. More research into how certain subgroups of MND patients transition between health states over time would be valuable to the literature [261]. Furthermore, clinical trial results should include how patients transition between health states in the trial period, rather than just reporting mean change in ALSFRS-R or its items. These analyses should report by both the Kings and MiToS staging system and perhaps also by the newer FT9 system if it is shown to be valid [255]. Other systems may emerge in the future that warrant consideration. While we report some results by an alternative staging system (MiToS) to the Kings ALS staging (our base case), this was limited and assumed the same hazard rate as used by CADTH for their analysis using the Kings ALS staging system. This assumption is likely to be favourable to edaravone in our MiToS staging analysis as the utility decrement resulting from transitions away from stage 0 in MiToS is higher than those away from Kings stage 1. More studies are needed to compare how different staging models affect the ICER estimates of new treatments for MND and how they can be used in combination to reduce structural uncertainty.

While the license application in Europe for edaravone has been withdrawn at the time of writing due to the concerns highlighted by the Committee for Medicinal Products for Human use (CHMP), this paper has highlighted some potential challenges of demonstrating cost-effectiveness of treatments for MND. The concerns of the CHMP included the short trial duration, no evidence on survival or respiratory function captured and that the control arm appeared to have more severe disease [253]. Whilst, the aim of this study was to provide an early economic analysis based on the available evidence, and it should be acknowledged that edaravone is available in some countries, such as the United States, Canada and Japan. It may also be the case that, with further clinical trials, edaravone may resubmit and receive a European/U.K license. As noted, the high drug and administration costs associated with edaravone, along with high background costs of MND care, makes meeting the £30,000 per QALY ICER threshold highly challenging. An analysis in this study showed that the ICER associated with zero drug costs and full administration costs was over £200,000 per QALY gained. These challenges may well be faced by new treatments for MND which emerge in the future. A report commissioned by NICE covers this and other potential challenges in more detail [262]. Administration costs of edaravone are relevant to this evaluation, so solutions are limited, however a clinical trial is currently underway to test the safety and efficacy of an oral form of edaravone, which could eliminate the high administration costs, although high drug costs are likely to still be an obstacle. Further challenges include the likelihood that despite MND being an aggressive fatal condition, treatments for MND may not be considered to meet NICE's end of life criteria, which would allow a higher willingness to pay threshold (up to £50,000 per QALY). The MND population size in the UK would also likely mean that any new MND treatments would be too large to be considered for NICE's highly specialised technology program (which allows a maximum ICER of at least £100,000 per QALY). There is a possibility that future treatments for small specific MND subgroups may meet this criteria (for example gene therapies which target specific mutations in the familial/inherited form of MND) if specialised centres are required to administer and monitor treatment.

The conclusions in the CADHT pharmacoeconomic report, while presented from a Canadian prespective, are not too dissimilar to the ones presented in this paper [245]. Our base case ICER is higher than the one reported in their analysis; however our inputs were different so direct comparisons are perhaps of limited value. In our analysis, the incremental QALY gain from edaravone using the Kings staging (as used in the CADHT analysis) lies between 0.06

and 0.3, the CADHT report states a range of 0.1 to 0.3, showing very similar QALY gain estimates. One key difference in assumptions between our base case analysis and the CADHT evaluation is the application of a constant treatment effect across all Kings stages in the CADHT analysis. That report also assumes a treatment effect resulting in reduced transitions to stage 4 and, indirectly, the death stage. We believe these assumptions to be highly uncertain based on the limited published evidence and clinical expectations and we prefer our assumption of treatment benefit (and use) in the early Kings stages (stages 1 and 2) [242,256].

The strengths of this study include the use of edaravone trial data and matched PRO-ACT cohort. Further to this, patient-level cost and utility data from the TONiC longitudinal study which reported these data from UK patients [6]. We have presented a wide range of one-way sensitivity analysis, explored a variety of different scenarios, in addition to using two prominent MND staging models. This has allowed us to investigate the parameters which have the biggest influence on the ICER calculation and explore some of the uncertainty surrounding the effectiveness of edaravone.

Our analysis comes with several limitations. Firstly, we did not have access to patient-level trial data or information on the distribution of patients across Kings stages over time. Therefore, we had to estimate both Kings stage at baseline and at 6 months (and beyond) using a matched PRO-ACT dataset. Secondly, the trial data does not inform survival or long-term effects on respiratory functioning, due to the short trial duration and relatively less severe MND population, our analysis relies on health state transition estimates from our matched PRO-ACT cohort for transitions after 6 months, which was limited in size. We were also only able to present a limited exploratory analysis using an alternative model, the MiToS model. This was due to a lack of information from the clinical trial on how patients may transition between MiToS stages. Another potential limitation of our paper is that we did not have data for caregiver utilities. MND is known to have a substantial impact on caregivers [207]. The lack of caregiver data is a common restriction in health economic models for many conditions. We also did not consider the disutility of the edaravone treatment regimen, but it is reasonable to assume that some disutility would be expected, given the need for infusions between 10-14 per 4-week cycle. Any disutility added to the model would increase the ICER (the CADTH evaluation also did not include this disutility). No adverse events were accounted for in the model either as not enough data on this was produced by the

edaravone trials. All our analyses are presented as deterministic results. While the CADTH analysis of edaravone for MND reported that results did not differ substantially when using probabilistic sensitivity analysis, such analysis would add further robustness to these results.

5.5 Conclusion

There is limited evidence for edaravone's clinical effectiveness in people with MND, with the pivotal trial only showing a benefit in people with less severe disease. In our study we show that cost-effectiveness results based on the treatment effect observed in a clinical trial indicates that the ICER associated with edaravone treatment is high. This can be expected due to the high cost of the drug and the administration costs along with the marginal estimated QALY gained. The analysis showed that even if edaravone drug costs were close to zero, the treatment may still not be considered cost-effective by NICE. This is due to the considerable administration costs. These analyses should be considered alongside the significant clinical uncertainties associated with edaravone. Despite the limitations described, this study provides useful cost-effectiveness analyses for decision-makers. While the manufacturer has currently withdrawn its license application, future potential MND treatments are likely to face some of the same challenges in demonstrating cost-effectiveness at usually accepted willingness-to-pay thresholds.

Chapter six

Discussion

The previous chapters have introduced the issues surrounding health technology assessments in MND and have presented novel research to add to a limited evidence base. The analyses carried out covered areas which are fundamental to estimating the value and cost-effectiveness of new treatments for MND. This chapter discusses the contributions of this thesis to the field with both the strengths and weaknesses of the research highlighted. A narrative is also given on areas where additional research may be warranted, and the potential future challenges are outlined.

6.1 Statement of principal findings

From the systematic review in chapter two, it is clear that there are considerable gaps in the evidence informing healthcare decision-making in MND. The review shows how previous studies have researched health economic aspects of MND, highlighting that methods used varied. It combined three different types of studies: health economic evaluations, cost and health utility and presented details on the current evidence base which exists regarding key parameters used in assessments of potential new treatments. The evidence gaps highlighted included limited numbers of studies reporting either cost or health utility outcomes in MND, particularly those which were presented by relevant health staging systems (some studies reported results by older MND disease staging systems no longer in common use). Similarly, the review also found a lack of health economic evaluations which report results using these accepted health staging systems. Further to this, the included studies in the review came from a range of settings, across several countries and regions and highlighted how parameters estimates can vary significantly by geographical location. The review highlighted the high levels of uncertainty in the current evidence base. The results presented throughout this thesis adds to the limited evidence base identified in that review and reports key information using relevant and accepted MND staging models.

A finding from chapter three shows that it is possible to estimate health utilities from the ALSFRS-R, the most used measure in MND clinical trials. The chapter investigated the various parts of the ALSFRS-R measure (items, domains and index) and tested their

suitability for mapping to the EQ-5D-5L. The results showed that the ALSFRS-R item and domains scores provided a better statistical fit to the ED-5D data that the ALSFRS-R index score. This finding is in line with previous studies which reported that the ALSFRS-R should be reported as a multidimensional score [33,34]. The study provides a method from which health utility data can be estimated, which should benefit health technology assessments in potential future treatments for MND when EQ-5D data has not been collected within a clinical trial. EQ-5D data are not routinely collected in MND trials. Providing a statistical link to the EQ-5D-5L from the ALSFRS-R allows preference-based utilities to be estimated. NICE has accepted utilities which have been mapped from another source and have issued guidance on this matter [92].

Another finding, from chapter four, is that health state utilities vary across health states and disease severity, with more progressed disease states associated with lower utility. The impact of MND on health-related is significant, with the average EQ-5D-5L utility of 0.57. which is comparable to the most severe stages of myasthenia gravis, or major trauma in frail populations, for example [263,264]. This chapter also showed that health state costs also, in general, increased with disease severity – as described by two commonly used health state staging systems (Kings and MiToS). Another finding was that key cost drivers are hospital admissions (around 40% of total costs) and community healthcare services. Analysis using both the Kings and MiToS staging systems together, in terms of health utilities and numbers in each combination of the stages across both systems, further adds to the evidence that these staging systems complement each other [58]. This is because the two staging systems focus on different aspects of the disease, with the Kings staging system focusing on the number of body regions affected and whether a tracheostomy or gastrostomy is required. The MiToS staging system focuses on the number of domains in which independence has been lost. Further to this, the Kings staging system is more sensitive to changes in earlier stages of MND, with the MiToS staging system sensitive in later stages. Bulbar onset was associated with a higher utility for a given health state in the analysis. This is interesting as bulbar onset is associated with a faster decline [265]

The economic evaluation of edaravone for the treatment of MND presented in chapter five shows that even at a zero price, edaravone is likely to be not cost-effective at conventional willingness to pay thresholds (£20,000 to £30,000 per QALY). This is primarily due to the cost of the intensive administration regime of edaravone, which is administered intravenously

10 to 14 days per month and the limited treatment effect of the drug coupled with the relatively limited effectiveness of edaravone. This is compared to standard care which includes riluzole, a drug which forms part of current standard care for MND, is given orally and has generic versions available which substantially reduces the acquisition costs of riluzole. Chapter five also highlights that the ICER estimate is sensitive to the various assumptions used to model long term effectiveness. In addition, the study provides a real-world example of how challenging it may be for new MND treatments which do not provide substantial health benefits, to demonstrate cost-effectiveness at usual willingness-to-pay thresholds [262].

6.2 Novel contributions

This body of work adds to a limited evidence base in health economic research regarding MND. Beyond that, it provides evidence across a range of health economic areas. Several pieces of research presented in the thesis are novel. A systematic review provides a foundation for this thesis and highlights areas which need more robust evidence generation. At the time of writing, this systematic review is the only one to be published that focuses on health economic evaluations, cost and health utility studies in MND.

Statistical mapping (or cross-walking) is becoming more commonly reported and used in the health economic literature [189]. Gaps in generic preference-based health utility may be addressed by disease-specific measures that can be used to estimate the missing data. A recent review of mapping studies highlighted that while the number of published mapping studies has increased over time, there were none presented for mapping from MND specific measures [189]. The statistical mapping analyses in chapter three presented the first study to attempt to map MND specific measures to the widely used EQ-5D-5L questionnaire. Various statistical methods and predictive variables were used, which allowed a broad analysis to be undertaken. Further to this, the study identified the thematical overlaps between the ALSFRS-R and EQ-5D-5L measures. It reported that the domains of pain and anxiety/depression, which is not covered in the ALSFRS-R, are reported to be relatively less severe in MND populations compared to the domains which are common to both measures. These findings came from analysing the domain responses of EQ-5D-5L in terms of the severity distributions. These findings have not been reported previously in the literature.

The health state costs and utilities study in chapter four provides data on key parameters within health economics and are fundamental elements of health economic models. This appears to be the first study to report health utility and costs/resource use in the UK using two well-known MND clinical staging systems. Further to this, the study reports heath utilities and the distributions of patients across the various combinations of Kings and MiToS staging systems, when both of these systems are used together. The usefulness of this analysis (combining health staging systems) has been recommended in previous research [40]. This study also presented the first health state utilities by the ALS utility Index, a preference-based measure which uses parts of the ALSFRS-R [174].

Chapter five presents what is believed to be the first health economic evaluation of edaravone as a treatment for MND in a UK setting. This analysis highlights some key drivers, which include drug costs, in incremental cost-effectiveness ratios (ICERs) calculations for new MND treatments. It shows that the administration costs associated with edaravone's intensive treatment regime means that is unlikely that edaravone could be seen as a cost-effective use of NHS resources in the UK based on current accepted thresholds used by NICE. The study also provides a substantial range of sensitivity analyses, including various scenarios, which helps to highlight the extent of the uncertainty around the ICER. The manufacturer has currently withdrawn the license application to the EMA at the time of writing, however the analysis presented is still of value, as it presents the cost-effectiveness of a treatment which may demonstrate similar levels of effectiveness (and perhaps costs) of future potential treatments for MND.

6.3 Comparison with other studies in health economics and MND

As identified in the systematic review carried out in chapter two, and in chapters 3 to 5, there have been other studies which have reported outcomes relevant to health economic parameters of MND. While the evidence base was found to be limited in key areas, some comparisons can be made between the research undertaken in this thesis and that which has been published previously.

As stated before, chapter four estimated health state costs and utilities for two well accepted and current health staging systems (Kings and MiToS). The systematic review identified 1 UK cost study which reported MND costs by health states [47]. This study was carried out in

1998, which explains the reason for the use of a health staging system that is no longer in use today [266]. This study also used clinical expert opinion to estimate resource use, which is not as robust as chapter four's patient completed questionnaire. This questionnaire also covered more cost categories. It is noteworthy that this study informed the initial economic evaluations of riluzole [267]. Chapter four showed that, in general, costs increased with disease severity. This finding is also reported in other studies in different settings and staging systems [268,269].

The finding that health state utilities decrease with disease severity has also been reported previously which confirms the findings of other studies on health state utilities in MND [270,271], however one of these studies used the previously mentioned out of date staging system to report health state utilities [269]. Further to this, chapter four provides some evidence to support the use of the EQ-5D-5L descriptive system, over that of the EQ-5D-3L. This is due to the evidence that the 5L measure reduces ceiling and flooring effects associated with the 3L measure, this finding is supported in the literature for other conditions [272,273]. One study was identified, in the systematic review in chapter 2, that reported EQ-5D-3L values for a UK population [271]. The utilities, as presented by the Kings ALS staging system, reported by this study were in general lower than those reported in chapter three. When considering the visual analogue scale (VAS) scores, they were similar in both studies. This perhaps suggests that the 5L measure reduces ceiling and flooring effects. No published study was identified which presented health state utilities using the ALS utility index (chapter three presented ALSUI by both Kings and MiToS staging systems).

As noted, the mapping study presented in chapter 3 was the first such one to focus on providing a statistical link between the ALSFRS-R and the EQ-5D-5L. The results of this analysis, in terms of accuracy (as measured in mean and absolute squared errors as is commonly used) is comparable to the range of reported statistical fits in mapping studies which have attempted to use disease-specific measures, used in other disease areas, to map to generic preference-based measures [189]. The best performing mapping model presented in chapter three using an Ordinary Least Squared (OLS) regression, which was identified as the best preforming method in a significant number of other mapping studies [189].

Chapter 5 presented a health economic evaluation of edaravone from a UK perspective. Other economic evaluations of drugs in MND have focused on riluzole, the only treatment currently

with a license to treat the condition. More recently, the Canadian Agency for Drugs and Technologies in Health (CADHT) reported results from an economic evaluation from a Canadian health payer perspective [245]. It was not possible to compare health state costs and utilities values used as the CADHT report did not provide this level of granularity, but a comparison can be made on the methods and modelling assumptions used. The CADHT analysis assumed a constant treatment effect of edaravone across each transition between health states and that edaravone would be used and effective when administered in all health states. The base case analysis in chapter five only assumed edaravone would be administered in less severe health states and did not directly reduce rates of tracheostomy or gastrotomy or directly improve survival, based on the observed clinical trial evidence [238]. This is likely part of the reason why the base case ICER presented in chapter 5 was higher than that estimated in the CADHT report. As analysis in chapter 5 was based on the observed data from the pivotal edaravone trial, it could be argued is a more relevant assumption to make. The analysis in chapter 5 estimates transitions based on changes in ALSFRS-R items, supplemented with a matched PRO-ACT cohort to estimate transition probabilities, whereas the CADHT based transition probabilities from a more general MND population. Chapter 5 also reports results using a variety of transitions to show the impact on the ICER estimate.

6.4 Strengths of the research

The research presented in the thesis benefits from several aspects. Chapter two presents a systematic review, which could be considered comprehensive and wide ranging as it included not only all published economic evaluations, but also included cost and health utility studies in MND. The report also offered a narrative on the studies identified, including comments on key methods used and the level of variability in outcomes. The review highlighted the need for methodologically robust evidence in these areas and provided a steer to the rest of the investigative chapters in the thesis.

The direct use of the TONiC dataset in chapters three and four ensures that these results are particularly relevant to a United Kingdom setting and should benefit future decision-making in regard to new treatments for MND [6]. The TONiC study is a the largest MND study in the UK covering quality of life in people with MND, with data from 636 patients used in this thesis, which is a significant proportion of the UK MND population (around 13-16%). This study was administered across 15 UK specialist MND sites and the baseline data from

TONiC used in this thesis was associated with a high questionnaire completion rate. The TONiC study included many pertinent data categories which had relevance to health economic considerations, including information on individual characteristics, resource use and both disease-specific measures (such as the ALSFRS-R [274]) and the EQ-5D-5L (generic preference-based measure) [275]. The richness and depth of the TONiC data used in this thesis is therefore a key strength of this thesis.

Thesis chapters two to five cover a range of health economic aspects which adds useful and up to date evidence for those undertaking economics evaluations for new treatments for MND, including those which inform health technology assessments of these treatments, by agencies such as NICE. Many aspects of this research link into the types of evidence that help analyses to comply with the guidance given by the NICE reference case, see chapter 1, table 1.1. This includes systematic reviewing to assess the evidence base, statistical mapping to address gaps in health-related quality of life data from MND clinical trials, up to date health state costs (from a health payer perspective) and health state utilities (from a UK cohort). In addition, the economic model in chapter 5 reports outcomes and analyses as outlined in the NICE reference case.

The statistical mapping study in chapter three used the various structures of the ALSFRS-R (most commonly used measure in MND trials) to test their ability to provide accurate estimates of EQ-5D-5L utilities. This ensured that a full range of models were investigated. The study also investigated the use of direct (to EQ-5D-5L utility tariff) and indirect mapping (to EQ-5D domains). The preferred model was comparable in terms of accuracy to those published in other neurological conditions and in other disease areas [189].

Chapter four was a detailed cost and health utility study, which provides costs from an NHS perspective and utility values from a UK population and evidence for the range of most essential parameters used in economic evaluations helps cover factors in healthcare provision decision-making. Utility values are presented by two preference-based health measures: one generic measure (EQ-5D-5L) and one disease-specific measure (ALSUI). Costs were presented by various categories, allowing key cost drivers to be identified (such as hospitalisations). Furthermore, this evidence was presented by two well accepted staging systems (Kings and MiToS), making these analyses appropriate for use in markov modelling, a commonly used method in economic evaluations. Evidence is also presented for the

distributions across the EQ-5D-5L domain responses, allowing comparisons to be made between on the thematic overlap between the EQ-5D-5L and the ALSFRS-R.

These chapters contribute to the sparse health economic literature for MND. The thesis presents results by up to date and well accepted disease-specific measures (namely the ALSFRS-R) and health staging models, which help make the analysis relevant to the current environment. Chapter five's economic evaluation of edaravone, the first drug approved for MND by in the FDA in 20 years, uses the health state costs and utilities from the study presented in chapter 4 to estimate relevant cost-effectiveness estimates for a UK population. The comparative clinical trial data is limited to only 6 months, with no deaths recorded in either arm [235]. This is likely to be a result of the selection of patients with less severe disease and the inclusion requirement of no respiratory impairment. Further to this, there were no transitions to the most severe health states as defined by both the Kings and MiToS staging systems. Despite this, chapter five presented methods, using the limited edaravone trial data and trial matched data extracted from the PRO-ACT dataset to estimate missing health state transition information [276]. This dataset was also used to estimate transitions beyond the end of the trial data, allowing an economic evaluation to be performed. This work also further demonstrated the value of the PRO-ACT dataset in economic evaluations in MND. The PRO-ACT dataset is a comprehensive dataset, used previously in MND research [277,278].

6.5 Weaknesses of the research

The research in this thesis was also limited by certain factors. The review is also limited by the small numbers of health economic, cost or health utilities studies published which focus on MND. This is a common issue with rare diseases, and a limitation of the evidence base more than the methods used. The mapping study specified in chapter four was limited to cross-sectional data from the TONiC study as no longitudinal data from this source is available at this time. It also maps to the EQ-5D-5L utility tariff which is not currently recommended by NICE [279]. Instead NICE, in 2019, recommended mapping from the EQ-5D-5L to the EQ-5D-3L utility tariff. The analysis in chapter three was guided at the time by the EQ-5D-5L England tariff which was recently developed by Devlin et al [274]. NICE does prefer the descriptive system of the EQ-5D-5L, as it adds sensitivity to each domain, but was not satisfied with the study underpinning the utility tariff. This statement from NICE came

after the analysis had been completed for chapter three. This adds uncertainty in the results from the mapping study described in the chapter. The estimation models produced in chapter 3 were unable to predict negative utilities (although negative utilities were only reported in 2.2% of MND patients in this study) and was less accurate when estimating utilities in more severe disease. In addition to this, the results of the mapping study were validated with internal data, which is common practice, but should ideally be confirmed using external data.

The health state costs and utilities study described in chapter five also did not use longitudinal data and had to use average costs for hospital inpatient stays, rather than costing by the number of nights spent in hospital, due to the data available. It should be noted that the resource use questionnaire, like all the TONiC study questionnaires, was designed before the work for this thesis commenced. Longitudinal data would have allowed results to reflect how costs and utilities change over time for individual patients. The study was also limited by the low number of observations in severe MiToS stages, therefore the costs and utilities in these stages are associated with more uncertainty. This limitation is due to the criteria of the most severe MiToS stages, requiring patients to have lost independence in three or more domains.

While chapter five presented the first cost-effectiveness analysis and results for edaravone from a UK perspective, it is limited by the short duration of clinical trial underpinning the analyses [235], and the need to estimate transitions to Kings stage 4 and death from an external source (PROACT database) as these transitions where not observed in the 6 months endpoint of the edaravone trial. Extrapolating beyond the end of trial data however is common practice, and this limitation of short edaravone trial data is due to the trial design in this case. The use of the PRO-ACT dataset involved matching the patients in that dataset to some of the restrictive inclusion criteria of the pivotal edaravone trial. While this helped enable the transition probabilities to be more reflective of this trial population, it could be argued that these transition probabilities are only relevant to this population and not (as least not fully) to other trial cohorts.

Another key weakness of the research is the lack of any inclusion of care giver quality of life considerations. With MND severely limiting independent living of those who develop the condition, the involvement of informal caregiving is very common. The burden of this is large, as demonstrated by some studies investigating this aspect of care [280,281]. Many health technology agencies now allow care giver considerations to form part of the evidence

base for decision-making in the provision of new treatments, and NICE has included caregiver health-related quality of life, where relevant, as part of its reference case. The reason for the lack of evidence for this area in this thesis is due to the TONiC study not including a questionnaire which could generate empirical data on carer quality of life. Again, the TONiC study was designed and started before work started on this thesis. Indeed, a recent systematic review did not find any questionnaires specifically designed to measure MND specific carer quality of life [282], although some generic measures have been designed to capture this aspect over a range of disease areas [283,284,285]. Changes in carer quality of life which result from the use of new potential treatments for MND can be considered relevant in the context of healthcare decision-making, but more evidence is needed to understand the impact the disease has on carer giver burden. Studies which use preference-based measures would be the most useful for inclusion in economic evaluations, to ensure that impacts on caregiver health-related quality of life is accounted for in appraisals of new potential treatments for MND.

As described through the thesis, clinical staging systems are becoming used more by health economists, those who design clinical trials and clinicians to classify key disease progression events. While the research in the thesis does provide results for two prominent staging systems (Kings and MiToS) research inevitably continues in this area. One newer staging system is the 'fine til 9' (FT9) system, which counts the number of domains of the ALSFRS-R in which the score is 9 or less [286]. This system benefits from being easily applied to ALSFRS-R data and appears to be sensitive to changes along the disease course [287]. Results are not presented for the FT9 system in this thesis due to timing. The publication which proposes the new system states that it appears to be sensitive to disease progression and, like the Kings ALS staging system, does not seem to result in backward transitions (which is deemed reflective of the progressive nature of MND) [286].

6.6 Challenges for health economic analysis and Motor Neurone Disease

While this thesis contributes several novel pieces of research in health economics and MND, it cannot provide a comprehensive evidence base alone. Research in MND can be limited by the relative rarity of the disease, and the fast-progressive nature of the condition can make gathering data a challenge. The severity of the disease in the latter stages also adds to the difficultly of data collection in these groups of patients. As shown in this thesis, data from

resources such as the TONiC and PRO-ACT datasets, has shown it is possible to collate data from regional and international sources to create large enough sample sizes to inform research. It is important that more international collaboration takes place so that sources, like those mentioned, can be developed.

There is a debate over the ability of the ALSFRS-R to capture the importance of specific changes in functioning. As this measure is not preference-based, each point decline in each item is weighted the same, regardless of their impact on health-related quality of life. The ALSFRS-R score can also be reported by domains, which may be 4 domains (bulbar, fine motor, gross motor, respiratory) or 3 domains (bulbar, motor, respiratory). Some studies have suggested that the scores index score is not as informative as using the domain scores of the measure. One development in this area has been the ALS utility index, a US preference-based study which is based on parts of the ALSFRS-R [174]. Chapter 2, while providing evidence that the ALSFRS-R item scores may be good candidates to map to the EQ-5D measure, it also highlighted that there are several health domains which are relevant to people with MND but are not captured in the EQ-5D utility tariff. These include communication, salivation, hand use and respiratory function. This highlights that the EQ-5D measure might not capture all benefits of new treatments.

As patient-level data was not available for changes in ALSFRS-R item scores, the economic evaluation in chapter five relied therefore on the limited group mean changes in ALSFRS-R items, with no baseline information provided in the trial publication. The use of the PRO-ACT database [276] assisted the analysis in chapter five, however future trials should report results in more detail so that researchers can interrogate these data in detail, including patient level data. One trial of a potential new treatment appears to have agreed to share data from an upcoming phase III trial [288]. Resources such as PRO-ACT could be used to provide a matched control arm for clinical trials when estimating how the comparator group transition between key health states over time. The resource includes a large number of longitudinal data level data, incorporating details such as ALSFRS-R item scores (which can be used for staging also), baseline characteristics, subgroup type and more.

The pivotal edaravone trial which underpinned its FDA approval had strict inclusion criteria, which when applied to a general MND population would result in the majority being excluded from the trial [235]. Indeed, the first phase III edaravone trial, which had a more

relaxed inclusion criteria, failed to show a significant difference in change in ALSFRS-R at the 6 months point [289]. If future trials of new potential treatments also enforce such stringent inclusion rules (those which have less severe stages of MND), this would create a large gap in the evidence base for these treatments. A reason put forward for such detailed inclusion criteria, is to have a greater opportunity to highlight clinical benefit over a short clinical trial period, another is that those with less severe disease are more likely to benefit from treatment. A study which looked at inclusion criteria of trials of MND treatments showed that inclusion criteria varied considerably across trials and the majority of MND patients are excluded [290]. In the case of edaravone, the FDA and other regulators have granted edaravone an authorisation for use within the entire MND population, with no restrictions based on severity of the condition. Therefore, this treatment could be given to MND populations in which edaravone has not been tested or been proven to provide clinical benefit, meaning there was no possibility of the treatment being considered cost-effective in these groups. Another issue with the edaravone trial was that it was short in duration, with only 6 months comparative evidence generated. The control arm in the edaravone trial declined by an average of 7.50 in terms of ALSFRS-R score over the 6-month period, which appears to be faster than reported in other trials [291]. The CHMP opinion also highlighted that the control group appeared to have more advanced disease at baseline compared to edaravone [292]. Further to this, the ALSFRS-R was used in the edaravone pre study phase to identify patients who had experience a -1 to -4 decline on the ALSFRS-R. This was another criticism of the study as this further reduced its generatability to the wider population. The CHMP highlighted other key issues such as the low numbers of patients in the trial and the lack of treatment effect when the placebo group were switched to edaravone treatment after 6 months. Some studies suggest that edaravone offers little to no benefit when used in broader MND population and that it would not be practical to enforce this requirement in clinical practice to identify those likely to benefit from treatment [293,294]. Other studies have noted that ALSFRS-R decline can vary with different baseline covariates, and this should be considered when making inclusion criteria for clinical trials [278]. A positive from the edaravone trials in MND is that it is possible that treatments may work in selected populations. Subgroup effects have been discussed in the literature previously [295]. These studies have found that factors such as the decline of ALSFRS-R curve, age and site of onset are some factors which may impact on prognosis and on the likelihood of these groups to respond to treatment [296,297,298] These discussions have highlighted the need to identify potential subgroups that may respond differently to the wider MND population.

As mentioned in the introduction chapter, it is unlikely that new treatments for the full (or near full) MND population would meet either NICE's end of life criteria or meet the criteria for the highly specialised technology process. This means that although future MND treatments may be associated with high ICER estimates, the normal NICE threshold range for treatments covering all MND types is likely to apply (£20,000 to £30,000 per QALY gained). Some treatments which are intended to treatment specific types of MND caused by mutations in particular genes may result in a target population that is small enough to meet this part of the Highly Specialised Technology (HST) criteria. These types of treatment may require a highly trained and specialised health professionals to administer and monitor treatment, which may mean that the number of centres which would provide this treatment may be limited, again meeting another important consideration for the NICE HST program. As stated in the introduction chapter, when a treatment is appraised through the NICE HST program the willingness-to-pay threshold is increased to £100,000 per QALY gained (and potentially up to £300,000 depending on amount of undiscounted QALYs gained) [299]. While there is debate around whether the HST process captures public preferences in relation to the funding of treatments for rare diseases (there is strong evidence to say it does not [300]), it is worth highlighting that some new very targeted (and likely very expensive) treatments for MND may be candidates for HST consideration.

Further to this, many potential future treatments may face challenges in demonstrating value for money. In addition to potentially high drug prices, other factors may also present issues, including those due to the nature of MND or due to the administration burden of the drug. A recent study highlighted 4 scenarios in which some treatments may not be considered cost-effective even when priced at £0, though it should be acknowledged that these situations can be more likely to arise when the costs of the treatment is relatively high and/or the treatment is only marginally effective (such as the edaravone case) [262]. MND presents considerable costs to the health service. This means that any MND treatment which prolongs life accumulates these costs in addition to the cost of the new treatment. If the QALY gains of a new treatment is outweighed by the extra cost, it will likely not be deemed cost-effective if this results the ICER estimate breaching a set threshold. Another scenario arises when treatments, like edaravone for example, which are intravenously administered or have an intensive frequent administration regime or both face significant associated costs. These costs come directly from the provision of the treatment and are included in economic evaluations.

As shown previously, healthcare costs increase with disease severity, and so increased time in these health stages would increase the ICER estimate [268,269]. Another possible scenario is a treatment extends life in more severe stages of MND, which leads to more high cost clinical events occurring, such as overnight hospital stays. A recent retrospective analysis of riluzole, using the well accepted Kings ALS staging system, showed that it extended survival more in the most severe stage of the condition more than in less severe stages [301].

One therapeutically promising avenue is the development of Advanced Therapy Medicinal Products (ATMPs), particularly gene therapies. Development in this area has been seen with treatments being developed for mutations in the SODI or C9orf72 genes, which make up a minority of the MND population. The costs of such treatments are very likely to be high [302]. This inevitably will lead to challenges in demonstrating cost-effectiveness and therefore potential barriers or delays to patient access. Gene therapies may offer an avenue to develop a safe and effective treatment or even a cure for the condition [303]. If treatments, such as gene therapies, offer substantial treatment benefit (above that of, for example, edaravone or treatments with similar limited effectiveness) then there are some considerations which are likely to become more relevant. For example, in the economic evaluation of edaravone on chapter 5, it was shown in the analysis that the source used for health state utilities (EQ-5D-5L, EQ-5D-3L or ALSUI) did not significantly impact the ICER estimate, despite the utility values for each of these sources being quite different. This was due to edaravone only offering limited QALY gains. However, if new treatments were to offer substantially more QALY gains, then the source (and values) used will likely have much more impact on the cost-effectiveness outcomes. The same logic holds for health state costs and the source used for that as these treatments will incur these costs if they do not cure the condition, but substantially prolong survival. In reality, changes in any of the modelling assumptions in chapter 5 are likely to impact on cost-effectiveness estimates more than they did in the analysis involving edaravone (or in treatments providing similar benefits to edaravone).

As referred to, caregivers can be significantly impacted by caring for those with MND. Inclusion of caregiver quality of life is not without challenges. Several studies present evidence that states the EQ-5D may not be appropriate to measure the quality of life impact of healthcare interventions on caregivers [304]. The use of the EQ-5D has been used to include caregiver quality of life in some NICE health technology appraisals [305]. The

advantage of using EQ-5D in caregiver populations is the ease of combining these utility values with those collected from patients receiving a new intervention. However, if the EQ-5D does not capture pertinent information in caregivers, then it may be appropriate to consider other measures which have been developed specially to be relevant to caregiver burden. Relatively few NICE technology appraisals have included caregiver utilities, but with more interest and research ongoing in this area, it is expected that more economic evaluations will include caregiver utilities [306].

Even when caregiver utilities are included in analysis, they can produce what may appear to be "counter-intuitive" results. These kinds of results can occur when a patient's condition impacts significantly on caregiver health utility and a new intervention prolongs the life of the patient but does not remove all caregiving aspects of the underlying condition. In this situation, the caregiver spends more time caring for the individual. Therefore, even if the intervention prolongs the patient's life or reduces caregiver burden, the longer time spent caregiving increases this burden overall. This occurred in a recent NICE appraisal for another severe neurological condition - spinal muscular atrophy (SMA), when including caregiver utilities increased the ICER estimate [307]. Despite the challenges of measuring, and including caregiver utilities in economic evaluations, a greater level of understanding on the impact on carers of people with MND would benefit the discussions and debate around health economics of new potential MND treatments.

6.7 Recommendations for research and reflection

Further research in several aspects of MND and health economics would be beneficial for assessing the value of future treatments. The weaknesses highlighted in this body of work may also be addressed with further research in this area.

As mentioned, this thesis is supported by the use of data from the TONiC study, a large UK based study which captures various data on quality of life in people with MND. Longitudinal data collection, of up to 5 years, is ongoing. This thesis use of the TONiC dataset was limited to a data cut of baseline data from 636 patients. Longitudinal data, such as that which the TONiC study may provide, would be useful to understand how the health utility and costs vary over the lifetime of the condition and how patients transition among relevant health states over time. It would also add to the results presented in this this thesis, for example the

mapping study in chapter three would benefit from longitudinal data, which would help predict EQ-5D values based on changes in ALSFRS-R scores, rather than estimating these values based on cross-section data.

More health technology assessment agencies internationally are increasingly interested in considering the impact of different conditions on carers and how their quality of life is impacted [308]. While it is noted in the literature that the inclusion of carer quality of life in health economic assessments is difficult and limited by the lack of evidence generated in this area, more data on the changes in the quality of life of carers of people with MND would be useful [309]. This could, and should, be done using the different levels of severity and clinical staging of the condition in mind. Particular focus should be given to commonly used clinical staging and measures [250,286], as these are most likely to be included in future health economic evaluations. An additional benefit of reporting carer health-related qualify of life by these staging systems is that it will allow the impact on this aspect by both the intervention and the comparator treatment - giving the incremental benefit. It is highly likely that the impact on carers is correlated with MND disease severity, but to date there are limited studies, and none specifically reporting quality-adjusted-life-year changes, a metric used in many health economics evaluations. While, to date, only a limited number of NICE appraisals have included caregiver health-related quality of life, it should be noted that some appraisals for neurological conditions (particularly multiple sclerosis) have included these [305].

While this thesis does provide data on costs and health utilities, which add to a limited evidence base, more research is needed to validate and add to these results. These parameters are essential in assessing the incremental benefits, and incremental costs, of any potential new treatments, particularly influential when significant survival and quality of life gains are accrued by a new treatment. More studies reporting these values, by relevant MND clinical stages, allows these estimates to be more robust and precise. This research would also allow the appropriateness of the EQ-5D in MND populations to be investigated further [309]. Chapter four has shown that EQ-5D utility values decrease with disease severity, which shows some face validity. This finding has also been reported in other studies using various MND staging systems. Chapter four also highlighted that the EQ-5D-5L may be more appropriate descriptive system to use than the EQ-5D-3L, as it may mitigate the flooring effects associated with the measure. Future study into this would be beneficial to confirm the

5L measure is indeed more appropriate to use in MND populations. Identification of other factors which impact on health utility, beyond clinical staging, in future studies may be useful in more accurately estimating health utility in MND patients. When NICE endorses a UK utility tariff, which a new study has been commissioned to do, results using this measure should be estimated in MND populations. While it is preferable to gain health utility measurements directly from patients responding to preference-based measures, clinical experts and caregivers have a role in validation of these results and providing input where there are gaps in the evidence. There may be additional outcomes that are important beyond those captured in the clinical staging models, evidence on these other factors, such as fatigue and communication for example, should be captured in trial data [310,311]. Additional evidence of how MND impacts aspects beyond health, such as well-being or capabilities, may also be helpful to gain more understanding of the burden the condition places on people [312]. As noted in chapter 4, health-related quality of life is severely impacted, but little empirical evidence is available to assess wider impacts.

More research is ongoing on identifying relevant prognostic factors which influence clinical outcomes and survival in MND [313,314]. Establishing more prognostic factors that impact the trajectories of patients during the progression of the condition, including how these factors can estimate when key functional decline milestones are met, can help understand how potential treatments may work in different MND subgroups [315]. For example, recent advances in potential treatments being developed for the some of those affected by certain mutations associated with the familial form of MND offers hope to a small but clinically identifiable subgroup [316]. While most treatments will likely benefit those with less advanced disease, treatments such as rasagiline may be more effective in those whose disease is fast progressing based on recent studies [317]. Registry data is likely to be useful in helping identify key information on different MND subgroups that may respond to various types of treatments being developed. One clear example of this is the Pooled Resource Open-Access ALS Clinical Trials (PRO-ACT) database used in chapter five in this thesis, and in several other studies [277,278]. As in the case of edaravone [235], initial clinical trial evidence failed to show statistically different results in some key outcomes, such as decline in ALSFRS-R score. When trial data was investigated more closely in this case, it was found that the treatment may work for selected subgroups. This may be a common feature of early trials of new MND treatments.

The ALSFRS-R is the most commonly used measure in MND trials and is recommended for inclusion in all MND trials [318]. However, more research on the merits of the questionnaire in terms of measuring the impact of changes in each of its items or domains on quality of life in people with MND. Some researchers have questioned the usefulness of the ALSFRS-R to capture all relevant aspects of changes in functionally and propose to find new ways of measuring decline related to MND over time [319,320]. It should be noted, however, that the MiToS and FT9 staging systems are directly based on the ALSFRS-R in its current format and the Kings staging system can be estimated accurately from this measure also. Any adaptions to the ALSFRS-R, or creation of a new preferred measure, may erase these links to clinical staging systems or create the new for newer ones, therefore thought should be given to this issue. New alternative measures may benefit from consideration of patient preferences of the various states of health which people with MND may experience. This would allow changes in functioning caused by the condition to be appropriately weighted.

Classifications of the disease and clinical staging systems have been shown to be informative, as shown in this thesis, in highlighting the clinically and economically important milestones in the disease. It should be remembered that MND progression can be heterogenous across patients and difficult to predict with certainty. The Kings and MiToS staging systems have shown value and may be used together to complement each other [40]. The new FT9 system also offers another way of describing disease progression [286]. In future research, thought should be given as to how best to incorporate these when assessing the benefits offered by new treatments. In addition, as has been noted in chapter one, timely diagnosis is important. Advancements in this area would also likely allow the potential of more clinical benefits from potential treatments, including ruling out diseases which mimic MND, and using biomarkers (which may also predict treatment effects) [321].

6.8 Conclusions

This chapter discussed the key findings identified from the analyses undertaken in chapters 2 to 5. It also outlined both the strengths and weaknesses of the research and provided a narrative on the challenges that may face new potential treatments for MND. Key strengths of the research is the generation of novel data, informing key economic and health-related quality of life parameters for use in health economic research in MND. The thesis provides a wide range of results, covering many aspects of MND as a disease and as a HTA topic. It

stressed the need for the research and how the outcomes reflected the aims set out in the introduction chapter. The overall picture is one that shows the work undertaken in this thesis should prove to add important information to a limited evidence base. This thesis applied accepted health economic methods, such as systematic reviewing, statistical mapping, health utility and cost data by health states and Markov modelling to generate data to use in health economic modelling of new MND treatments. In addition, this thesis has, through investigating key parameters, highlighted some important issues and considerations in terms of evidence generation and economic/clinical uncertainties. By presenting these issues, the thesis provides a valuable foundation for future research.

The novel research in chapters 2 to 5 in this thesis were designed around the aim of providing more robust evidence for HTA for new treatments of MND. The objectives set out to achieve that aim were:

- Highlight the current evidence base of health economic evidence in MND populations and detail the methodology used in the identified studies and provide a narrative on areas of uncertainty (chapter 2)
- Provide a statistical link from a commonly used MND disease-specific measure to the preference-based EQ-5D-5L measure (chapter 3)
- Present health state costs and utilities by accepted MND health staging systems from a UK perspective (chapter 4)
- Estimate the clinical and cost-effectiveness of edaravone, a new potential treatment for MND, from a UK health payer perspective. In addition, provide a narrative on the likely challenges that new treatments for MND will face in demonstrating cost-effectiveness (chapter 5)

As shown, there are clearly challenges facing any assessment of MND treatments. These stem from the need to extrapolate long term outcomes from trials which are usually short in duration. Another challenge is the potential need to use certain assumptions regarding these outcomes, such as treatment starting and stopping rules and assumptions regarding clinical benefits at various disease stages and subgroups. These assumptions can significantly change the cost-effectiveness estimates and therefore the perceived value of a treatment for MND.

Uncertainty in long term outcomes will be higher in those treatments which may provide potential cures or significant health and survival gains.

There are reasons for hope, however. As outlined in chapter 1, there are several potential treatments currently in clinical trials for use in MND populations. Current treatment options for MND are extremely limited and any additions to the treatment pathway will be welcomed. Clinical staging models, as used in this thesis, have been developed and are broadly accepted, which provide the foundations for cost-effectiveness analysis. These models can also be used to account, to some extent, for the heterogeneity inherent over the course of MND. While in this thesis, in chapter 5, the Kings ALS staging system was chosen for the base case analysis (as was the case for the CADHT analysis). It should be noted that another two staging systems have been developed (MiToS and FT9) which describe the progression of MND differently. These staging systems can be used to reduce some of the structural uncertainty in analysis. The use of datasets such as TONiC, PRO-ACT and other MND registries will further help to reduce uncertainties in the evidence base.

While there is more research to be carried out and challenges to face, it is hoped that the research presented in this thesis will prove useful to those involved in estimating the value of new MND treatments.

References

1. Ng L, Khan F, Young CA, et al. Symptomatic treatments for amyotrophic lateral sclerosis/motor neuron disease. Cochrane Database Syst Rev. 2017 Jan 10;1(1):CD011776. doi: 10.1002/14651858.CD011776.pub2
2. Chad DA, Bidichandani S, Bruijn L, et al. Funding agencies and disease organizations: resources and recommendations to facilitate ALS clinical research. Amyotroph Lateral Scler Frontotemporal Degener. 2013 May;14 Suppl 1:62-6.
3. Simon NG, Huynh W, Vucic S, et al. Motor neuron disease: current management and future prospects. Intern Med J. 2015 Oct;45(10):1005-13
4. Kanning K, Kaplan A, Henderson C. Motor Neuron Diversity in Development and Disease. Annu Rev Neurosci. 2010;33:409-40.
5. Ginsberg G, Lowe S. Cost effectiveness of treatments for amyotrophic lateral sclerosis: a review of the literature. Pharmacoeconomics. 2002;20(6):367-87
6. Trajectories of Outcomes in Neurological Conditions (TONiC). https://tonic.thewaltoncentre.nhs.uk/tonic-mnd Accessed 15 June 2020
7. Milinis K, Tennant A, Mills RJ, et al; TONiC study group. Development and validation of Spasticity Index-Amyotrophic Lateral Sclerosis. Acta Neurol Scand. 2018 Jul;138(1):47-54
8. Schlüter DK, Tennant A, Mills R, et al. Risk factors for social withdrawal in amyotrophic lateral sclerosis/motor neurone disease. Amyotroph Lateral Scler Frontotemporal Degener. 2018 Nov;19(7-8):591-598
9. Atassi N, Berry J, Shui A, et al. The PRO-ACT database: design, initial analyses, and predictive features. Neurology. 2014;83(19):1719-1725
10. Writing Group; Edaravone (MCI-186) ALS 19 Study Group. Safety and efficacy of edaravone in well defined patients with amyotrophic lateral sclerosis: a randomised, double-blind, placebo-controlled trial. Lancet Neurol. 2017;16(7):505-512
11. Al-Chalabi A, Hardiman O. The epidemiology of ALS: a conspiracy of genes, environment and time. Nat Rev Neurol. 2013 Nov;9(11):617-28. doi: 10.1038/nrneurol.2013.203.
12. Wais V, Rosenbohm A, Petri S, Kollewe K, et al. The concept and diagnostic criteria of primary lateral sclerosis. Acta Neurol Scand. 2017 Sep;136(3):204-211.

13. Pinto WBVR, Debona R, Nunes PP, et al. Atypical Motor Neuron Disease variants: Still a diagnostic challenge in Neurology. Rev Neurol (Paris). 2019 Apr;175(4):221-232. doi: 10.1016/j.neurol.2018.04.016. Epub 2019 Mar 4.
14. Hogden A, Foley G, Henderson RD, et al. Amyotrophic lateral sclerosis: improving care with a multidisciplinary approach. J Multidiscip Healthc. 2017;10:205-215.
15. Alonso A, Logroscino G, Jick SS, Hernán MA. Incidence and lifetime risk of motor neuron disease in the United Kingdom: a population-based study. Eur J Neurol. 2009;16(6):745-751.
16. Motor Neurone Disease association. MND registery of England, Wales and Northern Ireland. Available at https://www.mndassociation.org/research/get-involved-in-research/take-part-in-research/mnd-register-of-england-wales-and-northern-ireland/ (last accessed 14th June 2020).
17. Riancho J, Bosque-Varela P, Perez-Pereda S, et al. The increasing importance of environmental conditions in amyotrophic lateral sclerosis. Int J Biometeorol. 2018 Aug;62(8):1361-1374. doi: 10.1007/s00484-018-1550-2.
18. Benatar M, Kurent J, Moore DH. Treatment for familial amyotrophic lateral sclerosis/motor neuron disease. Cochrane Database Syst Rev. 2009;(1):CD006153.
19. Talbott EO, Malek AM, Lacomis D. The epidemiology of amyotrophic lateral sclerosis. Handb Clin Neurol. 2016;138:225-38
20. Foster LA, Salajegheh MK. Motor Neuron Disease: Pathophysiology, Diagnosis, and Management. Am J Med. 2019;132(1):32-37.
21. Young CA, Ealing J, McDermott C, et al. The relationships between symptoms, disability, perceived health and quality of life in amyotrophic lateral sclerosis/motor neuron disease. Amyotroph Lateral Scler Frontotemporal Degener. 2019;20(5-6):317-327.
22. Creemers H, Grupstra H, Nollet F, et al. Prognostic factors for the course of functional status of patients with ALS: a systematic review. J Neurol. 2015;262(6):1407-1423.
23. Westeneng HJ, Debray TPA, Visser AE, et al. Prognosis for patients with amyotrophic lateral sclerosis: development and validation of a personalised prediction model. Lancet Neurol. 2018;17(5):423-433
24. Geevasinga N, Howells J, Menon P, van den Bos M, Shibuya K, Matamala JM, Park SB, Byth K, Kiernan MC, Vucic S. Amyotrophic lateral sclerosis diagnostic index: Toward a personalized diagnosis of ALS. Neurology. 2019 Feb 5;92(6):e536-e547

25. Bäumer D, Talbot K, Turner MR. Advances in motor neurone disease. J R Soc Med. 2014;107(1):14-21.
26. Crooks BR, Miller RG, Swash M, Munsat TL; World Federation of Neurology Research Group on Motor Neuron Diseases. El Escorial revisited: revised criteria for the diagnosis of amyotrophic lateral sclerosis. Amyotroph Lateral Scler Other Motor Neuron Disord. 2000 Dec;1(5):293-9
27. Crockford C, Newton K, Lonergan K, et al. ALS-Specific Cognitive and Behavior Changes Associated with Advancing Disease Stage in ALS. 2018 Neurology 91 (15) E1370-E1380
28. Paynter C, Cruice M, Mathers S, Gregory H, Vogel AP. Communication and cognitive impairments and health care decision making in MND: A narrative review. J Eval Clin Pract. 2019;25(6):1182-1192
29. Aoun SM, Deas K, Kristjanson LJ, Kissane DW. Identifying and addressing the support needs of family caregivers of people with motor neurone disease using the Carer Support Needs Assessment Tool. Palliat Support Care. 2017;15(1):32-43.
30. Chen X, Wei QQ, Chen Y, Cao B, et al. Clinical Staging of Amyotrophic Lateral Sclerosis in Chinese Patients. Front Neurol. 2018 Jun 19;9:442
31. Leigh PN, Swash M, Iwasaki Y, et al. Amyotrophic lateral sclerosis: a consensus viewpoint on designing and implementing a clinical trial. Amyotroph Lateral Scler Other Motor Neuron Disord. 2004;5(2):84-98
32. Rooney J, Burke T, Vajda A, Heverin M, Hardiman O. What does the ALSFRS-R really measure? A longitudinal and survival analysis of functional dimension subscores in amyotrophic lateral sclerosis. J Neurol Neurosurg Psychiatry. 2017;88(5):381-385.
33. Bakker LA, Schröder CD, van Es MA, et al. Assessment of the factorial validity and reliability of the ALSFRS-R: a revision of its measurement model. J Neurol. 2017;264(7):1413-1420. doi:10.1007/s00415-017-8538-4
34. Franchignoni F, Mandrioli J, Giordano A, Ferro S; ERRALS Group. A further Rasch study confirms that ALSFRS-R does not conform to fundamental measurement requirements. Amyotroph Lateral Scler Frontotemporal Degener. 2015;16(5-6):331-337
35. Castrillo-Viguera C, Grasso DL, Simpson E, et al. Clinical significance in the change of decline in ALSFRS-R. Amyotroph Lateral Scler. 2010;11(1-2):178-80.

36. Silva-Illanes N, Espinoza M. Critical Analysis of Markov Models Used for the Economic Evaluation of Colorectal Cancer Screening: A Systematic Review. Value Health. 2018 Jul;21(7):858-873
37. Mohindru B, Turner D, Sach T, et al. Health economic modelling in Cystic Fibrosis: A systematic review. J Cyst Fibros. 2019 Jul;18(4):452-460
38. Balendra R, Jones A, Jivraj N, et al. Use of clinical staging in amyotrophic lateral sclerosis for phase 3 clinical trials. J Neurol Neurosurg Psychiatry. 2015;86(1):45-9.
39. Tramacere I, Dalla Bella E, Chiò A, et al. The MITOS system predicts long-term survival in amyotrophic lateral sclerosis. J Neurol Neurosurg Psychiatry. 2015;86(11):1180-1185
40. Fang T, Al Khleifat A, Stahl DR, et al. Comparison of the King's and MiToS staging systems for ALS. Amyotroph Lateral Scler Frontotemporal Degener. 2017;18(3-4):227-232.
41. Thakore NJ, Lapin BR, Kinzy TG, et al. Deconstructing progression of amyotrophic lateral sclerosis in stages: a Markov modeling approach. Amyotroph Lateral Scler Frontotemporal Degener. 2018;19(7-8):483-494.
42. Balendra R, Al Khleifat A, Fang T, Al-Chalabi A. A standard operating procedure for King's ALS clinical staging. Amyotroph Lateral Scler Frontotemporal Degener. 2019 May;20(3-4):159-164
43. Martin S, Trevor-Jones E, Khan S, et al. The benefit of evolving multidisciplinary care in ALS: a diagnostic cohort survival comparison. Amyotroph Lateral Scler Frontotemporal Degener. 2017;18(7-8):569-575.
44. Rooney J, Byrne S, Heverin M, et al. A multidisciplinary clinic approach improves survival in ALS: a comparative study of ALS in Ireland and Northern Ireland. J Neurol Neurosurg Psychiatry. 2015;86(5):496-501
45. Chiò A, Mora G, Lauria G. Pain in amyotrophic lateral sclerosis. Lancet Neurol. 2017;16(2):144-157
46. Radunovic A, Annane D, Rafiq MK, et al . Mechanical ventilation for amyotrophic lateral sclerosis/motor neuron disease. Cochrane Database Syst Rev. 2017;10(10):CD004427
47. Turner MR, Faull C, McDermott CJ, Nickol AH, Palmer J, Talbot K. Tracheostomy in motor neurone disease. Pract Neurol. 2019 Dec;19(6):467-475
48. National Institute of Health and Care Excellence (NICE). Clinicial guideline 42: Motor Neurone Disease. 2020. Available at

https://www.nice.org.uk/guidance/ng42/evidence/full-guideline-pdf-2361774637 (accessed 29th May 2021)

49. Bensimon G, Lacomblez L, Meininger V. A controlled trial of riluzole in amyotrophic lateral sclerosis. ALS/Riluzole Study Group. N Engl J Med. 1994;330(9):585-591.
50. Fang T, Al Khleifat A, Meurgey JH, et al. Stage at which riluzole treatment prolongs survival in patients with amyotrophic lateral sclerosis: a retrospective analysis of data from a dose-ranging study. Lancet Neurol. 2018;17(5):416-422
51. Petrov D, Mansfield C, Moussy A, Hermine O. ALS Clinical Trials Review: 20 Years of Failure. Are We Any Closer to Registering a New Treatment? Front Aging Neurosci. 2017 Mar 22;9:68
52. Takei K, Watanabe K, Yuki S, et al. Edaravone and its clinical development for amyotrophic lateral sclerosis. Amyotroph Lateral Scler Frontotemporal Degener. 2017;18(sup1):5-10.
53. Palumbo JM, Hubble J, Apple S, et al. Post-hoc analyses of the edaravone clinical trials Study 16 and Study 19: a step toward more efficient clinical trial designs in amyotrophic lateral sclerosis. Amyotroph Lateral Scler Frontotemporal Degener. 2019;20(5-6):421-431
54. Takahashi F, Takei K, Tsuda K, Palumbo J. Post-hoc analysis of MCI186-17, the extension study to MCI186-16, the confirmatory double-blind, parallel-group, placebo-controlled study of edaravone in amyotrophic lateral sclerosis. Amyotroph Lateral Scler Frontotemporal Degener. 2017;18(sup1):32-39.
55. Writing Group; Edaravone (MCI-186) ALS 19 Study Group. Safety and efficacy of edaravone in well defined patients with amyotrophic lateral sclerosis: a randomised, double-blind, placebo-controlled trial. Lancet Neurol. 2017;16(7):505-512
56. Hardiman O, Al-Chalabi A, Brayne C, et al. The changing picture of amyotrophic lateral sclerosis: lessons from European registers. J Neurol Neurosurg Psychiatry. 2017;88(7):557-563
57. Fortuna A, Gizzi M, Bello L, et al. Safety and efficacy of edaravone compared to historical controls in patients with amyotrophic lateral sclerosis from North-Eastern Italy. J Neurol Sci. 2019;404:47-51.
58. Abraham A, Nefussy B, Fainmesser Y, et al. Early post-marketing experience with edaravone in an unselected group of patients with ALS. Amyotroph Lateral Scler Frontotemporal Degener. 2019;20(3-4):260-263

59. Jackson C, Heiman-Patterson T, Kittrell P, et al. Radicava (edaravone) for amyotrophic lateral sclerosis: US experience at 1 year after launch. Amyotroph Lateral Scler Frontotemporal Degener. 2019 Nov;20(7-8):605-610
60. European Medicines Agency. Radicava: Withdrawal of the marketing authorisation application. Available at https://www.ema.europa.eu/en/medicines/human/withdrawn-applications/radicava (last accessed 15th June 2020)
61. Miller RG, Appel SH. Introduction to supplement: the current status of treatment for ALS. Amyotroph Lateral Scler Frontotemporal Degener. 2017;18(sup1):1-4.
62. Motor Neurone Disease Association. Available at https://www.mndassociation.org/research/ (last accessed 15th June 2021)
63. Motor Neurone Disease Association. Treatment trials. Available at https://www.mndassociation.org/research/about-mnd-research/clinical-trials/treatment-trials/ (last accessed 15th June 2021)
64. Heike J. Wobst, Korrie L. Mack, et al (2020) The clinical trial landscape in amyotrophic lateral sclerosis—Past, present, and future. Medicinal Research Reviews 40:4, pages 1352-1384.
65. Chen Y, Wang H, Ying Z, Gao Q. Ibudilast enhances the clearance of SOD1 and TDP-43 aggregates through TFEB-mediated autophagy and lysosomal biogenesis: The new molecular mechanism of ibudilast and its implication for neuroprotective therapy. Biochem Biophys Res Commun. 2020 May 21;526(1):231-238
66. Clinical trials.gov. Evaluation of MN-166 (Ibudilast) for 12 Months Followed by an Open-label Extension for 6 Months in Patients With ALS (COMBAT-ALS). Available at https://clinicaltrials.gov/ct2/show/NCT04057898 (last accessed September 2021)
67. Paganoni S, Macklin EA, Hendrix S, et al. Trial of Sodium Phenylbutyrate-Taurursodiol for Amyotrophic Lateral Sclerosis. N Engl J Med. 2020 Sep 3;383(10):919-930
68. Cappella M, Ciotti C, Cohen-Tannoudji M, Biferi MG. Gene Therapy for ALS-A Perspective. Int J Mol Sci. 2019 Sep 6;20(18):4388
69. National Human Genome Institute. Gene Therapies, available at https://www.genome.gov/genetics-glossary/Gene-Therapy (last accessed June 2021)
70. Miller TM, Pestronk A, David W, et al. An antisense oligonucleotide against SOD1 delivered intrathecally for patients with SOD1 familial amyotrophic lateral sclerosis: a phase 1, randomised, first-in-man study. Lancet Neurol. 2013 May;12(5):435-42.

doi: 10.1016/S1474-4422(13)70061-9. Epub 2013 Mar 29. Erratum in: Lancet Neurol. 2013 May;12(5):423

71. Al-Zaidy SA, Kolb SJ, Lowes L, et al. AVXS-101 (Onasemnogene Abeparvovec) for SMA1: Comparative Study with a Prospective Natural History Cohort. J Neuromuscul Dis. 2019;6(3):307-317
72. Maynard A, Kanavos P. Health economics: an evolving paradigm. Health Econ. 2000 Apr;9(3):183-90
73. Kolm S. A historical introduction to normative economics. Social Choice and Welfare 2000 17(4)707-738
74. McGuire A, Parkin D, Hughes D, Gerard K. Econometric analyses of national health expenditures: can positive economics help to answer normative questions? Health Econ. 1993 Jul;2(2):113-26.
75. Culyer AJ, Chalkidou K. Economic Evaluation for Health Investments En Route to Universal Health Coverage: Cost-Benefit Analysis or Cost-Effectiveness Analysis? Value Health. 2019 Jan;22(1):99-103
76. Harvey HB, Sotardi ST. The Pareto Principle. J Am Coll Radiol. 2018 Jun;15(6):931
77. Rogowski W, Payne K, Schnell-Inderst P, et al. Concepts of 'personalization' in personalized medicine: implications for economic evaluation. Pharmacoeconomics. 2015 Jan;33(1):49-59
78. Buchanan J, Wordsworth S. Welfarism versus extra-welfarism: can the choice of economic evaluation approach impact on the adoption decisions recommended by economic evaluation studies? Pharmacoeconomics. 2015 Jun;33(6):571-9.
79. Anand P. Capabilities and health. J Med Ethics. 2005 May;31(5):299-303.
80. X Bravo Vergel Y, Sculpher M. Quality-adjusted life years. Pract Neurol. 2008 Jun;8(3):175-82. doi: 10.1136/pn.2007.140186
81. Brouwer WB, Culyer AJ, van Exel NJ, Rutten FF. Welfarism vs. extra-welfarism. J Health Econ. 2008 Mar;27(2):325-38. doi: 10.1016/j.jhealeco.2007.07.003
82. Coast J, Smith RD, Lorgelly P. Welfarism, extra-welfarism and capability: the spread of ideas in health economics. Soc Sci Med. 2008 Oct;67(7):1190-8
83. Birch S, Donaldson C. Valuing the benefits and costs of health care programmes: where's the 'extra' in extra-welfarism? Soc Sci Med. 2003 Mar;56(5):1121-33
84. Huynh E, Coast J, Rose J, Kinghorn P, Flynn T. Values for the ICECAP-Supportive Care Measure (ICECAP-SCM) for use in economic evaluation at end of life. Soc Sci Med. 2017;189:114-128.

85. Brazier J, Tsuchiya A. Improving Cross-Sector Comparisons: Going Beyond the Health-Related QALY. Appl Health Econ Health Policy. 2015;13(6):557-565.
86. Neumann PJ, Goldie SJ, Weinstein MC. Preference-based measures in economic evaluation in health care. Annu Rev Public Health. 2000;21:587-611.
87. Dolan P. Modeling valuations for EuroQol health states. Med Care 1997; 35(11): 1095-108.
88. Pressler SJ, Eckert GJ, Morrison GC, et al. Evaluation of the Health Utilities Index Mark-3 in heart failure. J Card Fail. 2011 Feb;17(2):143-50
89. Lins L, Carvalho FM. SF-36 total score as a single measure of health-related quality of life: Scoping review. SAGE Open Med. 2016 Oct 4;4
90. Baird K. High Out-of-Pocket Medical Spending among the Poor and Elderly in Nine Developed Countries. Health Serv Res. 2016 Aug;51(4):1467-88
91. McCabe C, Claxton K, Culyer AJ. The NICE cost-effectiveness threshold: what it is and what that means. Pharmacoeconomics. 2008;26(9):733-744.
92. National Institute of Health and Care Excellence (NICE). Guide to the methods of technology appraisal 2013
93. Severens JL, Milne RJ. Discounting health outcomes in economic evaluation: the ongoing debate. Value Health. 2004 Jul-Aug;7(4):397-401
94. National Institute of Health and Social Care. Interim Process and Methods of the Highly Specialised Technologies Programme. 2017.
95. National Institute of Health and Social Care. Riluzole for the treatment of Motor Neurone Disease, Single Technology Appraisal TA20. 2001.
96. National Institute of Health and Social Care. Appraising life-extending end of life treatments. Available at https://www.nice.org.uk/guidance/gid-tag387/documents/appraising-life-extending-end-of-life-treatments-paper2
97. Oh J, An JW, Oh SI, et al. Socioeconomic costs of amyotrophic lateral sclerosis according to staging system. Amyotroph Lateral Scler Frontotemporal Degener. 2015 Jun;16(3-4):202-8
98. Davis, S. Assessing Technologies that are not cost-effective at a zero price. Decision Support Unit, ScHARR, University of Sheffield. Available at http://nicedsu.org.uk/methods-development/not-cost-effective-at-0/
99. Henrard S, Arickx F. Negotiating prices of drugs for rare diseases. Bull World Health Organ. 2016 Oct 1;94(10):779-781

100. European Medicines Agency. Orphan Drugs. Available at EMA orphan drugs: https://www.ema.europa.eu/en/human-regulatory/overview/orphan-designation-overview (last accessed September 2021)
101. Bourke SM, Plumpton CO, Hughes DA. Societal Preferences for Funding Orphan Drugs in the United Kingdom: An Application of Person Trade-Off and Discrete Choice Experiment Methods. Value Health. 2018;21(5):538-546.
102. Mentzakis E, Stefanowska P, Hurley J. A discrete choice experiment investigating preferences for funding drugs used to treat orphan diseases: an exploratory study. Health Econ Policy Law. 2011 Jul;6(3):405-33
103. Wiss J, Levin L-Å, Andersson D, Tinghög G. Prioritizing rare diseases: Psychological effects influencing medical decision making. Medical Decision Making, 2017. Published online ahead of print
104. Johnston CA, Stanton BR, Turner MR, et al. Amyotrophic lateral sclerosis in an urban setting: a population based study of inner city London. J Neurol. 2006;253(12):1642-1643.
105. Alonso A, Logroscino G, Jick SS, Hernán MA. Incidence and lifetime risk of motor neuron disease in the United Kingdom: a population-based study. Eur J Neurol. 2009;16(6):745-751.
106. Hughes DA, Poletti-Hughes J. Profitability and Market Value of Orphan Drug Companies: A Retrospective, Propensity-Matched Case-Control Study. PLoS One. 2016;11(10):e0164681
107. Simoens S, Cassiman D, Dooms M, Picavet E. Orphan drugs for rare diseases: is it time to revisit their special market access status?. Drugs. 2012;72(11):1437-1443.
108. Kiernan MC, Vucic S, Cheah BC, et al. Amyotrophic lateral sclerosis. Lancet. 2011;377(9769):942-955.
109. Hogg, KE, Goldstein LH, Leigh PN. The psychological impact of motor neurone disease. Psychol Med. 1994;24(3):625-32.
110. Miyashita M, Narita Y, Sakamoto A, et al. Health-related quality of life among community-dwelling patients with intractable neurological diseases and their caregivers in Japan. Psychiatry Clin Neurosci. 2011;65(1):30-8.
111. Chiò A, Logroscino G, Traynor BJ, Collins J, Simeone JC, Goldstein LA, White LA. Global epidemiology of amyotrophic lateral sclerosis: a systematic review of the published literature. Neuroepidemiology. 2013;41(2):118-30.

112. Leigh PN, Abrahams S, Al-Chalabi A, Ampong MA, Goldstein LH, Johnson J, Lyall R, Moxham J, Mustfa N, Rio A, Shaw C, Willey E; King's MND Care and Research Team. The management of motor neurone disease. J Neurol Neurosurg Psychiatry. 2003;74 Suppl 4:iv32-iv47.

113. Centre for Reviews and Dissemination. Systematic reviews: CRD's guidance for undertaking reviews in health care. York: University of York; 2009. https://www.york.ac.uk/media/crd/Systematic_Reviews.pdf (Accessed Aug 3, 2016).

114. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ. 2009;339:b2535.

115. International Monetary Fund (IMF). Exchange Rate Archives. http://www.imf.org/external/np/fin/data/param_rms_mth.aspx (Accessed 17th October 2016)

116. Curtis L, Burns A. Unit Costs of Health and Social Care 2015. http://www.pssru.ac.uk/project-pages/unit-costs/2015/index.php (Accessed 17th October 2016).

117. Alanazy H, White C, Korngut L. Diagnostic yield and cost-effectiveness of investigations in patients presenting with isolated lower motor neuron signs. Amyotroph Lateral Scler Frontotemporal Degener. 2014;15(5-6):414-9.

118. Vitacca M, Paneroni M, Trainini D, Bianchi L, Assoni G, Saleri M, Gilè S, Winck JC, Gonçalves MR. At Home and on Demand Mechanical Cough Assistance Program for Patients With Amyotrophic Lateral Sclerosis. Am J Phys Med Rehabil. 2010;89(5):401-6.

119. Cruis K, Chernew M and Brown D. The cost-effectiveness of early noninvasive ventilation for ALS patients. BMC Health Serv Res. 2005;5:58.

120. Tavakoli M. Disease progression in amyotrophic lateral sclerosis. Identifying the cost-utility of riluzole by disease stage. Eur J Health Econ. 2002;3(3):156-65.

121. Tavakoli M, Malek M. The cost utility analysis of riluzole for the treatment of amyotrophic lateral sclerosis in the UK. J Neurol Sci. 2001;191(1-2):95-102.

122. National Institute for Health and Care Excellence. Riluzole (Rilutek) for the treatment of Motor Neurone Disease (TA20), 2001.

123. Bryan S, Barton P, Burls A. The clinical effectiveness and cost effectiveness of riluzole for motor neurone disease – an update. Birmingham: West Midlands

Development and Evaluations Service, Department of Public Health and Epidemiology. University of Birmingham. 2000.

124. Stewart A, Sandercock J, Bryan S, Hyde C, Barton PM, Fry-Smith A, Burls A. The clinical effectiveness and cost-effectiveness of riluzole for motor neurone disease: a rapid and systematic review. Health Technol Assess. 2001;5(2):1-97.

125. Messori A, Trippoli S, Becagli P, Zaccara G. Cost effectiveness of riluzole in amyotrophic lateral sclerosis. Italian Cooperative Group for the Study of Meta-Analysis and the Osservatorio SIFO sui Farmaci. Pharmacoeconomics. 1999;16(2):153-63.

126. Ackerman SJ, Sullivan EM, Beusterien KM, Natter HM, Gelinas DF, Patrick DL. Cost effectiveness of recombinant human insulin-like growth factor I therapy in patients with ALS. Pharmacoeconomics. 1999;15(2):179-95.

127. Ringel SP, Woolley JM, Culebras A. Economic analysis of neurological services. Eur J Neurol. 1999;6 Suppl 2:s21-s24.

128. Gray AM. ALS/MND and the perspective of health economics. J Neurol Sci. 1998;160 Suppl 1:S2-5.

129. Ginsberg GM, Lev B. Cost-benefit analysis of riluzole for the treatment of amyotrophic lateral sclerosis. Pharmacoeconomics. 1997;12(5):578-84.

130. Booth-Clibborn N, Best L, Stein K. Riluzole for motor neurone disease. Development and Evaluation Committee Report No.73. Wessex Institute for Health Research and Development. 1997.

131. Chilcott J, Golightly P, Jefferson D et al. The use of riluzole in the treatment of amyotrophic lateral sclerosis. Sheffield: Trent Institute for Health Services Research. University of Leicester, Nottingham and Sheffield. 1997.

132. Boylan K, Levine T, Lomen-Hoerth C, Lyon M, Maginnis K, Callas P, Gaspari C, Tandan R; ALS Center Cost Evaluation W/Standards & Satisfaction (Access) Consortium. Prospective study of cost of care at multidisciplinary ALS centers adhering to American Academy of Neurology (AAN) ALS practice parameters. Amyotroph Lateral Scler Frontotemporal Degener. 2015;17(1-2):119-27.

133. Oh J, An JW, Oh SI, Oh KW, Kim JA, Lee JS, Kim SH. Socioeconomic costs of amyotrophic lateral sclerosis according to staging system. Amyotroph Lateral Scler Frontotemporal Degener. 2015;16(3-4):202-8

134. Obermann M, Lyon M. Financial cost of amyotrophic lateral sclerosis: A case study. Amyotroph Lateral Scler Frontotemporal Degener. 2015;16(1-2):54-7.

135. Connolly S, Heslin C, Mays I, Corr B, Normand C, Hardiman O. Health and social care costs of managing amyotrophic lateral sclerosis (ALS): An Irish perspective. Amyotroph Lateral Scler Frontotemporal Degener. 2015;16(1-2):58-62.
136. Athanasakis K, Kyriopoulos II, Sideris M, Rentzos M, Evdokimidis J, Kyriopoulos J. Investigating the economic burden of ALS in Greece: A cost-of-illness approach. Amyotroph Lateral Scler Frontotemporal Degener. 2015;16(1-2):63-4.
137. Gladman M, Dharamshi C, Zinman L. Economic burden of amyotrophic lateral sclerosis: A Canadian study of out-of-pocket expenses. Amyotroph Lateral Scler Frontotemporal Degener. 2014;15(5-6):426-32.
138. Larkindale J, Yang W, Hogan PF, Simon CJ, Zhang Y, Jain A, Habeeb-Louks EM, Kennedy A, Cwik VA. Cost of illness for neuromuscular diseases in the United States. Muscle Nerve. 2014;49(3):431-8.
139. Kang SC, Hwang SJ, Wu PY, Tsai CP. The utilization of hospice care among patients with motor neuron diseases: The experience in Taiwan from 2005 to 2010. J Chin Med Assoc. 2013;76(7):390-4.
140. Jennum P, Ibsen R, Pedersen SW, Kjellberg J. Mortality, health, social and economic consequences of amyotrophic lateral sclerosis: A controlled national study. J Neurol. 2013;260(3):785-93.
141. Muscular Dystrophy Association. Cost of Amyotrophic Lateral Sclerosis, Muscular Dystrophy, and Spinal Muscular Atrophy in the United States. Muscular Dystrophy Association, The Lewin Group Inc. 2012. https://www.mda.org/sites/default/files/Cost_Illness_Report.pdf (Accessed Aug 3, 2016)
142. Lopes de Almeida JP, Pinto A, Pinto S, Ohana B, de Carvalho M. Economic cost of home-telemonitoring care for BiPAP-assisted ALS individuals. Amyotroph Lateral Scler. 2012;13(6):533-7.
143. Vitacca M, Comini L, Assoni G, Fiorenza D, Gilè S, Bernocchi P, Scalvini S. Tele-assistance in patients with amyotrophic lateral sclerosis: Long term activity and costs. Disabil Rehabil Assist Technol. 2012;7(6):494-500.
144. Ward AL, Sanjak M, Duffy K, Bravver E, Williams N, Nichols M, Brooks BR. Power wheelchair prescription, utilization, satisfaction, and cost for patients with Amyotrophic lateral sclerosis: Preliminary data for evidence-based guidelines. Arch Phys Med Rehabil. 2010;91(2):268-72.

145. Schepelmann K, Winter Y, Spottke AE, Claus D, Grothe C, Schröder R, Heuss D, Vielhaber S, Mylius V, Kiefer R, Schrank B, Oertel WH, Dodel R. Socioeconomic burden of amyotrophic lateral sclerosis, myasthenia gravis and facioscapulohumeral muscular dystrophy. J Neurol. 2010;257(1):15-23.

146. López-Bastida J, Perestelo-Pérez L, Montón-Alvarez F, Serrano-Aguilar P, Alfonso-Sanchez JL. Social economic costs and health-related quality of life in patients with amyotrophic lateral sclerosis in Spain. Amyotroph Lateral Scler. 2009;10(4):237-43.

147. Elman LB, Stanley L, Gibbons P, McCluskey L. A cost comparison of hospice care in Amyotrophic lateral sclerosis and lung cancer. Am J Hosp Palliat Care. 2006;23(3):212-6.

148. Forshew DA, Bromberg MB. A survey of clinicians' practice in the symptomatic treatment of ALS. Amyotroph Lateral Scler Other Motor Neuron Disord. 2003;4(4):258-63.

149. Wasner M, Klier H, Borasio GD. The use of alternative medicine by patients with amyotrophic lateral sclerosis. J Neurol Sci. 2001;191(1-2):151-4.

150. Lechtzin N, Wiener CM, Clawson L, Chaudhry V, Diette GB. Hospitalization in amyotrophic lateral sclerosis: Causes, costs, and outcomes. Neurology. 2001;56(6):753-7.

151. Munsat TL, Rivière M, Swash M, Leclerc C. Economic burden of amyotrophic lateral sclerosis in the United Kingdom. J Med Econ. 1998;1(1-4):235-45.

152. Klein LM, Forshew DA. The economic impact of ALS. Neurology. 1996;47(4 Suppl 2):S126-9.

153. Sevick MA, Kamlet MS, Hoffman LA, Rawson I. Economic cost of home-based care for ventilator-assisted individuals. Chest. 1996;109(6):1597-606.

154. Moss AH, Oppenheimer EA, Casey P, Cazzolli PA, Roos RP, Stocking CB, Siegler M. Patients with amyotrophic lateral sclerosis receiving long-term mechanical ventilation. Advance care planning and outcomes. Chest. 1996;110(1):249-55.

155. Kiebert GM, Green C, Murphy C, Mitchell JD, O'Brien M, Burrell A, Leigh PN. Patients' health-related quality of life and utilities associated with different stages of amyotrophic lateral sclerosis. J Neurol Sci. 2001;191(1-2):87-93

156. Jones AR, Jivraj N, Balendra R, Murphy C, Kelly J, Thornhill M, Young C, Shaw PJ, Leigh PN, Turner MR, Steen IN, McCrone P, Al-Chalabi A. Health utility

decreases with increasing clinical stage in amyotrophic lateral sclerosis. Amyotroph Lateral Scler Frontotemporal Degener. 2014;15(3-4):285-91.

157. Riviere M, Meininger V, Zeisser P, Munsat T. An analysis of extended survival in patients with amyotrophic lateral sclerosis treated with riluzole. Arch Neurol. 1998;55(4):526-8.

158. Lacomblez L, Bensimon G, Leigh PN, Guillet P, Powe L, Durrleman S, Delumeau JC, Meininger V. A confirmatory dose-ranging study of riluzole in ALS. Neurology. 1996;47(6 Suppl 4):S242-50.

159. Bensimon G, Lacomblez L, Meininger V. A controlled trial of riluzole in amyotrophic lateral sclerosis. ALS/Riluzole Study Group. N Engl J Med. 1994;330(9):585-91.

160. Lai EC, Felice KJ, Festoff BW, Gawel MJ, Gelinas DF, Kratz R, Murphy MF, Natter HM, Norris FH, Rudnicki SA. Effect of recombinant human insulin-like growth factor I on progression of ALS: a placebo-controlled study. Neurology. 1997;49(6):1621-30.

161. Bradley W. A controlled trial of recombinant methionyl human BDNF in ALS: The BDNF Study Group (Phase III). Neurology. 1999 Apr 22;52(7):1427-33.

162. Latimer N. NICE DSU Technical Support Document 14: Survival Analysis for Economic Evaluations alongside Clinical Trials – Extrapolation with Patient-Level Data Report by the Decision Support Unit; 2014.

163. Henriques A, Pitzer C, Schneider A. Neurotrophic Growth Factors for the Treatment of Amyotrophic Lateral Sclerosis: Where Do We Stand? Front Neurosci. 2010;4:32.

164. Mitsumoto H. ALS Clinical Trials https://psg-mac43.ucsf.edu/als/Mitsumoto,%20H%20(AAN)%208BS-006-97.pdf (Accessed Aug 3, 2016)

165. Goutman SA, Chen KS, Feldman EL. Recent advances and the future of stem cell therapies in Amyotrophic lateral sclerosis. Neurotherapeutics. 2015;12(2):428-48.

166. Scarrott JM, Herranz-Martín S, Alrafiah AR, Shaw PJ, Azzouz M. Current developments in gene therapy for amyotrophic lateral sclerosis. Expert Opin Biol Ther. 2015;15(7):935-47.

167. Al-Janabi H, Flynn TN, Coast J. QALYs and Carers. Pharmacoeconomics. 2011;29(12):1015-23.

168. Rowen D, Dixon S, Hernández-Alava M, Mukuria C. Estimating informal care inputs associated with EQ-5D for use in economic evaluation. Eur J Health Econ. 2016;17(6):733-44.
169. Tranmer JE, Guerriere DN, Ungar WJ, Coyte PC. Valuing patient and caregiver time: a review of the literature. Pharmacoeconomics. 2005;23(5):449-59.
170. Epton J, Harris R, Jenkinson C. Quality of life in amyotrophic lateral sclerosis/motor neuron disease: A structured review. Amyotroph Lateral Scler. 2009;10(1):15-26.
171. Jenkinson C, Peters M, Bromberg MB. Quality of life measurement in neurodegenerative and related conditions. Cambridge: Cambridge University Press, 2011.
172. Janssen MF, Pickard AS, Golicki D, Gudex C, Niewada M, Scalone L, Swinburn P, Busschbach J. Measurement properties of the EQ-5D-5L compared to the EQ-5D-3L across eight patient groups: A multi-country study. Qual Life Res. 2013;22(7):1717-27.
173. Greene ME, Rader KA, Garellick G, Malchau H, Freiberg AA, Rolfson O. The EQ-5D-5L improves on the EQ-5D-3L for health-related quality-of-life assessment in patients undergoing total hip Arthroplasty. Clin Orthop Relat Res. 2015;473(11):3383-90.
174. Beusterien K, Leigh N, Jackson C, Miller R, Mayo K, Revicki D. Integrating preferences into health status assessment for amyotrophic lateral sclerosis: The ALS utility index. Amyotroph Lateral Scler Other Motor Neuron Disord. 2005;6(3):169-76.
175. Goldstein LH, Adamson M, Jeffrey L, Down K, Barby T, Wilson C, Leigh PN. The psychological impact of MND on patients and carers. J Neurol Sci. 1998;160 Suppl 1:S114-21.
176. Goldstein LH, Adamson M, Barby T, Down K, Leigh PN. Attributions, strain and depression in carers of partners with MND: A preliminary investigation. J Neurol Sci. 2000;180(1-2):101-6.
177. Lerum SV, Solbrække KN, Frich JC. Family caregivers' accounts of caring for a family member with motor neurone disease in Norway: A qualitative study. BMC Palliat Care. 2016;15:22.

178. Hawton A, Shearer J, Goodwin E, Green C. Squinting through layers of fog: assessing the cost effectiveness of treatments for multiple sclerosis. Appl Health Econ Health Policy. 2013;11(4):331-41.

179. Knapp M, Iemmi V, Romeo R. Dementia care costs and outcomes: a systematic review. Int J Geriatr Psychiatry. 2013;28(6):551-61.

180. Van Es MA, Hardiman O, Chio A, et al. Amyotrophic lateral sclerosis. Lancet 2017;390(10107):2084-2098

181. Miller RG, Mitchell JD, Moore DH. Riluzole for amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND). Cochrane Database Syst Rev. 2012;(3):CD001447.

182. Miller RG, Jackson CE, Kasarskis EJ, et al. Practice Parameter update: The care of the patient with amyotrophic lateral sclerosis: Multidisciplinary care, symptom management, and cognitive/behavioural impairment (an evidence-based review). Neurology 2009; 73 (15):1227-1233.

183. Zwicker J, Qureshi D, Talarico R, Bourque P, Scott M, Chin-Yee N, Tanuseputro P. Dying of amyotrophic lateral sclerosis: Health care use and cost in the last year of life. Neurology. 2019 Dec 3;93(23):e2083-e2093.

184. Longworth L, Rowen D. Mapping to obtain EQ-5D utility values for use in NICE health technology assessments. Value Health. 2013;16(1):202-10.

185. Brazier J, Ara R, Rowen, D, et al. A Review of Generic Preference-Based Measures for Use in Cost-Effectiveness Models. PharmacoEconomics 2017;35(Suppl 1):21-31.

186. Jones A, Jivraj N, Balendra R, et al. Health utility decreases with increasing clinical stage in amyotrophic lateral sclerosis. Amyotroph Lateral Scler Frontotemporal Degener 2014;15(3-4):285-291.

187. Kiebert GM, Green C, Murphy C, et al. Patients' health-related quality of life and utilities associated with different stages of amyotrophic lateral sclerosis. J Neurol Sci 2001;191(1–2):87-93. NOW 155

188. NICE (2013). Process and Methods: Guide to the methods of technology appraisal available at https://www.nice.org.uk/process/pmg9 (last accessed 24th March 2017)

189. Dakin H. Review of studies mapping from quality of life or clinical measures to EQ-5D: an online database. Health Qual Life Outcomes. 2013;11:151.

190. Petrou S, Rivero-Arias O, Dakin H, et al. The MAPS Reporting Statement for Studies Mapping onto Generic Preference-Based Outcome Measures: Explanation and Elaboration. Pharmacoeconomics. 2015;33(10):993-1011.

191. Wailoo AJ, Hernandez-Alava M, Manca A, et al. Mapping to Estimate Health-State Utility from Non–Preference-Based Outcome Measures: An ISPOR Good Practices for Outcomes Research Task Force Report. Value Health 2017;20(1):18-27.

192. Dams J, Klotsche J, Bornschein B, et al. Mapping the EQ-5D index by UPDRS and PDQ-8 in patients with Parkinson's disease. Health and Quality of Life Outcomes 2013;11:35.

193. Sidovar MF, Limone BL, Lee S, et al. Mapping the 12-item multiple sclerosis walking scale to the EuroQol 5-dimension index measure in North American multiple sclerosis patients. BMJ Open 2013;3(5):e002798.

194. Cedarbaum JM, Stambler N, Malta E, et al. The ALSFRS-R: a revised ALS functional rating scale that incorporates assessments of respiratory function. BDNF ALS Study Group (Phase III). J Neurol Sci 1999;169(1-2):13-21.

195. Leigh PN, Swash M, Iwasaki Y, et al. Amyotrophic lateral sclerosis: a consensus viewpoint on designing and implementing a clinical trial. Amyotroph Lateral Scler Other Motor Neuron Disord 2004;5(2):84-98.

196. Beusterien K, Leigh N, Jackson C, et al. Integrating preferences into health status assessment for amyotrophic lateral sclerosis: the ALS Utility Index. Amyotroph Lateral Scler Other Motor Neuron Disord 2005;6(3):169-176. NOW 174

197. Devlin NJ, Shah KK, Feng Y, et al. Valuing health-related quality of life: An EQ-5D-5L value set for England. Health Econ 2017 Aug 22. doi: 10.1002/hec.3564.

198. Franchignoni F, Mora G, Giordano A, et al. Evidence of multidimensionality in the ALSFRS-R Scale: a critical appraisal on its measurement properties using Rasch analysis. J Neurol Neurosurg Psychiatry 2013;84(12):1340-1345.

199. Bradley S, Galer MD, Jensen MP. Development and preliminary validation of a pain measure specific to neuropathic pain: The Neuropathic Pain Scale. Neurology 1997;48(2):332-338.

200. Gibbons C, Mills RJ, Thornton EW, et al. Rasch analysis of the Hospital Anxiety and Depression scale (HADS) for use in motor neurone disease. Health Qual Life Outcomes 2011;9(1):82-90.

201. Zigmond AS and Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand. 1983;67(6):361-370.

202. McDonald JF, Moffitt A. The Uses of Tobit Analysis. Rev Econ Stat 1980;62(2):318-321.
203. R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. 2013.
204. Vrieze S. Model selection and psychological theory: a discussion of the differences between the Akaike information criterion (AIC) and the Bayesian information criterion (BIC). Psychol Methods 2012;17(2):228-243.
205. Chiò A, Logroscino G, Traynor BJ, et al. Global epidemiology of amyotrophic lateral sclerosis: a systematic review of the published literature. Neuroepidemiology 2013;41(2):118-130. NOW 111
206. Chiò A, Gauthier A, Montuschi A, et al. A cross sectional study on determinants of quality of life in ALS. J Neurol Neurosurg Psychiatry 2004;75(11):1597-1601.
207. Brown RH, Al-Chalabi A. Amyotrophic Lateral Sclerosis. N Engl J Med. 2017;377(2):162-72.
208. Munsat TL, Rivière M, Swash M, et al. Economic burden of amyotrophic lateral sclerosis in the United Kingdom. J Med Econ. 1998;1(1-4):235-45.
209. Bravver E, Sanjak M, Brooks B. Disease Severity and Disease Trajectory of Amyotrophic Lateral Sclerosis (ALS) Patients at Frist Clinic Visit Measured Prospectively with "ALS Dashboard" – A Six-Domain (Cognition, Affect, Bulbar, Respiratory, Arm, Leg) Staging System – Comparison of Two Cohorts (P07.088). Neurology. 2013;80(Supplement 7.088).
210. Rivere M, Meininger V, Zeisser P, et al. An analysis of extended survival in patients with amyotrophic lateral sclerosis treated with riluzole. Arch Neurol. 1998;55(4):526-8.
211. Roche JC, Rojas-Garcia R, Scott KM, et al. A proposed staging system for amyotrophic lateral sclerosis. Brain. 2012;135(Pt 3):847-52.
212. Tramacere I, Dalla Bella E, Chiò A, et al. The MITOS system predicts long-term survival in amyotrophic lateral sclerosis. J Neurol Neurosurg Psychiatry. 2015;86(11):1180-5.
213. Briggs A, Sculpher M. An introduction to Markov modelling for economic evaluation. Pharmacoeconomics. 1998;13(4):397-409.

214. Cedarbaum JM, Stambler N, Malta E, et al. The ALSFRS-R: a revised ALS functional rating scale that incorporates assessments of respiratory function. BDNF ALS Study Group (Phase III). J Neurol Sci 1999;169(1-2):13-21.

215. Leigh PN, Swash M, Iwasaki Y, et al. Amyotrophic lateral sclerosis: a consensus viewpoint on designing and implementing a clinical trial. Amyotroph Lateral Scler Other Motor Neuron Disord 2004;5(2):84-98.

216. Rooney J, Burke T, Vajda A, et al. What does the ALSFRS-R really measure? A longitudinal and survival analysis of functional dimension subscores in amyotrophic lateral sclerosis. J Neurol Neurosurg Psychiatry 2017;88:381-5.

217. Balendra R, Jones A, Jivraj N, et al. Use of clinical staging in amyotrophic lateral sclerosis for phase 3 clinical trials. J Neurol Neurosurg Psychiatry. 2015;86(1):45-9.

218. Devlin NJ, Shah KK, Feng Y, Mulhern B, van Hout B. Valuing health-related quality of life: An EQ-5D-5L value set for England. Health Econ. 2018;27(1):7-22.

219. Beusterien K, Leigh N, Jackson C, et al. Integrating preferences into health status assessment for amyotrophic lateral sclerosis: the ALS Utility Index. Amyotroph Lateral Scler Other Motor Neuron Disord. 2005;6(3):169-76. NOW 174

220. Marson AG, Al-Kharusi AM, Alwaidh M, et al. The SANAD study of effectiveness of valproate, lamotrigine, or topiramate for generalised and unclassifiable epilepsy: an unblinded randomised controlled trial. Lancet. 2007;369(9566):1016-26.

221. Database of Instruments for Resource Use Measurement (DIRUM). http://www.dirum.org (Accessed 19th September 2018).

222. Franchignoni F, Mora G, Giordano A, et al. Evidence of multidimensionality in the ALSFRS-R Scale: a critical appraisal on its measurement properties using Rasch analysis. J Neurol Neurosurg Psychiatry. 2013;84:1340-5.

223. Department of Health and Social care (2017). NHS reference costs 2016-17.

224. Curtis L, Burns A. (2017) Unit Costs of Health and Social care 2017, University of Kent, Canterbury. https://doi.org/10.22024/UniKent/01.02/65559 (Accessed 30th October 2018).

225. Curtis L. (2010) Unit Costs of Health and Social Care 2010, Personal Social Services Research Unit, University of Kent, Canterbury.

226. R Core Team (2013). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL http://www.R-project.org/ (Accessed 30th October 2018).

227. Chiò A, Logroscino G, Traynor BJ, et al. Global epidemiology of amyotrophic lateral sclerosis: a systematic review of the published literature. Neuroepidemiology 2013;41(2):118-30. NOW 111

228. Gumber A, Ramaswamy B, Ibbotson R, Ismail M, Thongchundee O, Harrop D, Allmark P, Rauf A. Economic, Social and Financial Cost of Parkinson's on Individuals, Carers and their Families in the UK. Project Report. Centre for Health and Social Care Research, Sheffield Hallam University. 2017. http://shura.shu.ac.uk/15930/ (Accessed 30th October 2018).

229. Jones C, Busse M, Quinn L, et al. The societal cost of Huntington's disease: are we underestimating the burden? Eur J Neurol. 2016;23(10):1588-90.

230. Fang T, Al Khleifat A, Stahl D, et al. Comparison of the King's and MiToS staging systems for ALS. Amyotroph Lateral Scler Frontotemporal Degener. 2017;18(3-4):227-32.

231. Galvin M, Corr B, Madden C, et al. Caregiving in ALS – a mixed methods approach to the study of burden. BMC Palliative Care. 2016;15(1):81.

232. Galvin M, Carney S, Corr B, et al. Needs of informal caregivers across the caregiving course in amyotrophic lateral sclerosis: a qualitative analysis. BMJ Open. 2018;8:e018721.

233. Tavakoli M. Disease progression in amyotrophic lateral sclerosis. Identifying the cost-utility of riluzole by disease stage. Eur J Health Econ. 2002;3(3):156–65. NOW 120

234. Riviere M, Meininger V, Zeisser P, Munsat T. An analysis of extended survival in patients with amyotrophic lateral sclerosis treated with riluzole. Arch Neurol. 1998;55(4):526–8.

235. Roche JC, Rojas-Garcia R, Scott KM, et al. A proposed staging system for amyotrophic lateral sclerosis. Brain. 2012;135(Pt 3):847-52.

236. Tramacere I, Dalla Bella E, Chiò A, et al. The MITOS system predicts long-term survival in amyotrophic lateral sclerosis. J Neurol Neurosurg Psychiatry. 2015;86(11):1180-5.

237. Fang T, Al Khleifat A, Meurgey JH et al. Stage at which riluzole treatment prolongs survival in patients with amyotrophic lateral sclerosis: a retrospective

analysis of data from a dose-ranging study. Lancet Neurol. 2018 May;17(5):416-422. doi: 10.1016/S1474-4422(18)30054-1. Epub 2018 Mar 7.

238. Edaravone writing group. Safety and efficacy of edaravone in well defined patients with amyotrophic lateral sclerosis: a randomised, double-blind, placebo-controlled trial. Lancet Neurol. 2017 Jul;16(7):505-512. doi: 10.1016/S1474-4422(17)30115-1. Epub 2017 May 15. NOW 10

239. Takei K, Watanabe K, Yuki S, Akimoto M, Sakata T, Palumbo J. Edaravone and its clinical development for amyotrophic lateral sclerosis. Amyotroph Lateral Scler Frontotemporal Degener. 2017 Oct;18(sup1):5-10.

240. Leigh PN, Swash M, Iwasaki Y, et al. Amyotrophic lateral sclerosis: a consensus viewpoint on designing and implementing a clinical trial. Amyotroph Lateral Scler Other Motor Neuron Disord 2004;5(2):84-98.

241. Abe K, Itoyama Y, Sobue G, et al. Confirmatory double-blind, parallel-group, placebo controlled study of efficacy and safety of edaravone (MCI-186) in amyotrophic lateral sclerosis patients. Amyotroph Lateral Scler Frontotemporal Degener. 2014;15(7–8):610–617.F

242. Takei K, Takahashi F, Liu S, et al. Post-hoc analysis of randomised, placebo-controlled, double-blind study (MCI186-19) of edaravone (MCI-186) in amyotrophic lateral sclerosis. Amyotroph Lateral Scler Frontotemporal Degener. 2017 Oct;18(sup1):49-54.

243. Hardiman O, Al-Chalabi A, Brayne C, et al. The changing picture of amyotrophic lateral sclerosis: lessons from European registers. J Neurol Neurosurg Psychiatry. 2017;88(7):557-563

244. European Medicines Agency. Radicava: Withdrawal of the marketing authorisation application. Available at https://www.ema.europa.eu/en/medicines/human/withdrawn-applications/radicava (last accessed 23rd July 2020)

245. Pharmacoeconomic Review Report: Edaravone (Radicava): (Mitsubishi Tanabe Pharma Corporation): Indication: For the treatment of Amyotrophic Lateral Sclerosis (ALS) [Internet]. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2019 Apr.

246. Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, Augustovski F, Briggs AH, Mauskopf J, Loder E; CHEERS Task Force. Consolidated

Health Economic Evaluation Reporting Standards (CHEERS) statement. J Med Econ. 2013;16(6):713-9.

247. Balendra R, Jones A, Jivraj N, et al. Estimating clinical stage of amyotrophic lateral sclerosis from the ALS Functional Rating Scale. Amyotroph Lateral Scler Frontotemporal Degener. 2014 Jun;15(3-4):279-84.

248. Atassi N, Berry J, Shui A, Zach N, Sherman A, Sinani E, Walker J, Katsovskiy I, Schoenfeld D, Cudkowicz M, Leitner M. The PRO-ACT database: design, initial analyses, and predictive features. Neurology. 2014 Nov 4;83(19):1719-25

249. Ferraro D, Consonni N, Fini A, et al. Amyotrophic lateral sclerosis: a comparison of two staging systems in a population-based study. Eur J Neurol. 2016 Sep;23(9):1426-32.

250. Fang T, Al Khleifat A, Stahl D, et al. Comparison of the King's and MiToS staging systems for ALS. Amyotroph Lateral Scler Frontotemporal Degener. 2017;18(3-4):227-32.

251. Moore A, Young CA, Hughes DA. Health Utilities and Costs for Motor Neurone Disease. Value Health. 2019 Nov;22(11):1257-1265. doi: 10.1016/j.jval.2019.05.011. Epub 2019 Aug 1. PMID: 31708062.

252. Jaiswal MK. Riluzole and edaravone: A tale of two amyotrophic lateral sclerosis drugs. Med Res Rev. 2019 Mar;39(2):733-748.

253. Department of Health and Social care (2019). NHS reference costs 2018-19

254. National Institute of Health and Care Excellence. Guide to the methods of technology appraisal 2013

255. Thakore NJ, Lapin BR, Kinzy TG, Pioro EP. Deconstructing progression of amyotrophic lateral sclerosis in stages: a Markov modeling approach. Amyotroph Lateral Scler Frontotemporal Degener. 2018 Nov;19(7-8):483-494.

256. Fortuna A, Gizzi M, Bello L, Martinelli I, Bertolin C, Pegoraro E, Corbetta M, Sorarù G; Edaravone Study Group. Safety and efficacy of edaravone compared to historical controls in patients with amyotrophic lateral sclerosis from North-Eastern Italy. J Neurol Sci. 2019 Sep 15;404:47-51

257. Jones A, Jivraj N, Balendra R, et al. Health utility decreases with increasing clinical stage in amyotrophic lateral sclerosis. Amyotroph Lateral Scler Frontotemporal Degener 2014;15(3-4):285-291.

258. Beusterien K, Leigh N, Jackson C, et al. Integrating preferences into health status assessment for amyotrophic lateral sclerosis: the ALS Utility Index. Amyotroph Lateral Scler Other Motor Neuron Disord 2005;6(3):169-176. NOW 174

259. Jackson C, Heiman-Patterson T, Kittrell P, Baranovsky T, McAnanama G, Bower L, Agnese W, Martin M. Radicava (edaravone) for amyotrophic lateral sclerosis: US experience at 1 year after launch. Amyotroph Lateral Scler Frontotemporal Degener. 2019 Nov;20(7-8):605-610.

260. Bäumer D, Talbot K, Turner MR. Advances in motor neurone disease. J R Soc Med. 2014;107(1):14-21.

261. Zou ZY, Zhou ZR, Che CH, Liu CY, He RL, Huang HP. Genetic epidemiology of amyotrophic lateral sclerosis: a systematic review and meta-analysis. J Neurol Neurosurg Psychiatry. 2017 Jul;88(7):540-549

262. Davis, S. Assessing Technologies that are not cost-effective at a zero price. Decision Support Unit, ScHARR, University of Sheffield. Available at http://nicedsu.org.uk/methods-development/not-cost-effective-at-0/

263. Barnett C, Bril V, Bayoumi AM. EQ-5D-5L and SF-6D health utility index scores in patients with myasthenia gravis. Eur J Neurol. 2019 Mar;26(3):452-459.

264. Tipping CJ, Bilish E, Harrold M, Holland AE, Chan T, Hodgson CL. The impact of frailty in critically ill patients after trauma: A prospective observational study. Aust Crit Care. 2020 May;33(3):228-235.

265. Young CA, Ealing J, McDermott C, et al. The relationships between symptoms, disability, perceived health and quality of life in amyotrophic lateral sclerosis/motor neuron disease. Amyotroph Lateral Scler Frontotemporal Degener. 2019;20(5-6):317-327.

266. Riviere M, Meininger V, Zeisser P, Munsat T. An analysis of extended survival in patients with amyotrophic lateral sclerosis treated with riluzole. Arch Neurol. 1998;55(4):526–8

267. Tavakoli M. Disease progression in amyotrophic lateral sclerosis. Identifying the cost-utility of riluzole by disease stage. Eur J Health Econ. 2002;3(3):156–65. NOW 120

268. Oh J, An JW, Oh SI, et al. Socioeconomic costs of amyotrophic lateral sclerosis according to staging system. Amyotroph Lateral Scler Frontotemporal Degener. 2015;16(3-4):202-208 NOW 133

269. Jennum P, Ibsen R, Pedersen SW, Kjellberg J. Mortality, health, social and economic consequences of amyotrophic lateral sclerosis: a controlled national study. J Neurol. 2013;260(3):785–93. NOW 140

270. Thakore NJ, Brittany L, Pioro EP. Health utility declines with advancing Fine'til 9 stage of ALS. Neurology 2019; 92 (15 Supplement)

271. Jones AR, Jivraj N, Balendra R, et al. Health utility decreases with increasing clinical stage in amyotrophic lateral sclerosis. Amyotroph Lateral Scler Frontotemporal Degener. 2014;15(3-4):285-291 NOW 156

272. Roudijk B, Donders ART, Stalmeier PFM; Cultural Values Group. Cultural Values: Can They Explain Differences in Health Utilities between Countries? Med Decis Making. 2019 Jul;39(5):605-616

273. Gandhi M, Ang M, Teo K, Wong CW, Wei YC, Tan RL, Janssen MF, Luo N. A vision 'bolt-on' increases the responsiveness of EQ-5D: preliminary evidence from a study of cataract surgery. Eur J Health Econ. 2020 Jun;21(4):501-511

274. Devlin NJ, Shah KK, Feng Y, Mulhern B, van Hout B. Valuing health-related quality of life: An EQ-5D-5L value set for England. Health Econ. 2018 Jan;27(1):7-22

275. Cedarbaum JM, Stambler N, Malta E, et al. The ALSFRS-R: a revised ALS functional rating scale that incorporates assessments of respiratory function. BDNF ALS Study Group (Phase III). J Neurol Sci 1999;169(1-2):13-21.

276. Atassi N, Berry J, Shui A, et al. The PRO-ACT database: design, initial analyses, and predictive features. Neurology. 2014;83(19):1719-1725

277. Braun N, Macklin EA, Sinani E, Sherman A, Weber M; Pooled Resource Open-Access ALS Clinical Trials Consortium. The revised El Escorial criteria "clinically probable laboratory supported ALS"-once a promising now a superfluous category? Amyotroph Lateral Scler Frontotemporal Degener. 2020 Feb;21(1-2):24-28

278. Jahandideh S, Taylor AA, Beaulieu D, et al. Longitudinal modelling to predict vital capacity in amyotrophic lateral sclerosis. Amyotroph Lateral Scler Frontotemporal Degener. 2018 May;19(3-4):294-302

279. National Institute of Health and Care Excellence. Position statement on use of the EQ-5D-5L value set for England. 2019 available at https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/technology-appraisal-guidance/eq-5d-5l (last accessed 23 August 2020)

280. Ugalde A, Mathers S, Hennessy Anderson N, Hudson P, Orellana L, Gluyas C. A self-care, problem-solving and mindfulness intervention for informal caregivers of people with motor neurone disease: A pilot study. Palliat Med. 2018;32(4):726-732
281. Kristjanson LJ, Aoun SM, Oldham L. Palliative care and support for people with neurodegenerative conditions and their carers. Int J Palliat Nurs. 2006;12(8):368-377
282. Page TE, Farina N, Brown A, Daley S, Bowling A, Basset T, Livingston G, Knapp M, Murray J, Banerjee S. Instruments measuring the disease-specific quality of life of family carers of people with neurodegenerative diseases: a systematic review. BMJ Open. 2017 Mar 29;7(3):e013611
283. Mei Y, Lin B, Li Y, Ding C, Zhang Z. Validity and reliability of Chinese version of Adult Carer Quality of Life questionnaire (AC-QoL) in family caregivers of stroke survivors. PLoS One. 2017 Nov 13;12(11):e0186680
284. Brouwer WB, van Exel NJ, van Gorp B, Redekop WK. The CarerQol instrument: a new instrument to measure care-related quality of life of informal caregivers for use in economic evaluations. Qual Life Res. 2006 Aug;15(6):1005-21
285. Hoefman RJ, van Exel J, Brouwer WBF. Measuring Care-Related Quality of Life of Caregivers for Use in Economic Evaluations: CarerQol Tariffs for Australia, Germany, Sweden, UK, and US. Pharmacoeconomics. 2017 Apr;35(4):469-478
286. Thakore NJ, Lapin BR, Kinzy TG, Pioro EP. Deconstructing progression of amyotrophic lateral sclerosis in stages: a Markov modeling approach. Amyotroph Lateral Scler Frontotemporal Degener. 2018;19(7-8):483-494
287. Thakore NJ, Brittany L, Pioro EP. Health utility declines with advancing Fine'til 9 stage of ALS. Neurology 2019; 92 (15 Supplement)
288. Miller T, Cudkowicz M, Shaw PJ, et al. Phase 1-2 Trial of Antisense Oligonucleotide Tofersen for SOD1 ALS. N Engl J Med. 2020 Jul 9;383(2):109-119
289. EDARAVONE (MCI-186) ALS 16 STUDY GROUP. A post-hoc subgroup analysis of outcomes in the first phase III clinical study of edaravone (MCI-186) in amyotrophic lateral sclerosis. Amyotroph Lateral Scler Frontotemporal Degener. 2017;18(sup1):11-19
290. Hardiman O, Al-Chalabi A, Brayne C, et al. The changing picture of amyotrophic lateral sclerosis: lessons from European registers. J Neurol Neurosurg Psychiatry. 2017;88(7):557-563

291. Mandrioli J, Biguzzi S, Guidi C, Sette E, Terlizzi E, Ravasio A, Casmiro M, Salvi F, Liguori R, Rizzi R, Pietrini V, Borghi A, Rinaldi R, Fini N, Chierici E, Santangelo M, Granieri E, Mussuto V, De Pasqua S, Georgoulopoulou E, Fasano A; ERRALS Group, Ferro S, D'Alessandro R. Heterogeneity in ALSFRS-R decline and survival: a population-based study in Italy. Neurol Sci. 2015 Dec;36(12):2243-52

292. Radicava: Withdrawal of the marketing authorisation application. European Medicines Agency. Available at https://www.ema.europa.eu/en/medicines/human/withdrawn-applications/radicava (last accessed 15th June 2020)

293. Fortuna A, Gizzi M, Bello L, et al. Safety and efficacy of edaravone compared to historical controls in patients with amyotrophic lateral sclerosis from North-Eastern Italy. J Neurol Sci. 2019;404:47-51

294. Abraham A, Nefussy B, Fainmesser Y, Ebrahimi Y, Karni A, Drory VE. Early post-marketing experience with edaravone in an unselected group of patients with ALS. Amyotroph Lateral Scler Frontotemporal Degener. 2019;20(3-4):260-263

295. Verber NS, Shepheard SR, Sassani M, McDonough HE, Moore SA, Alix JJP, Wilkinson ID, Jenkins TM, Shaw PJ. Biomarkers in Motor Neuron Disease: A State of the Art Review. Front Neurol. 2019 Apr 3;10:291

296. Daghlas I, Lever TE, Leary E. A retrospective investigation of the relationship between baseline covariates and rate of ALSFRS-R decline in ALS clinical trials. Amyotroph Lateral Scler Frontotemporal Degener. 2018 May;19(3-4):206-211.

297. Thakore NJ, Lapin BR, Pioro EP; Pooled Resource Open-Access ALS Clinical Trials Consortium. Trajectories of impairment in amyotrophic lateral sclerosis: Insights from the Pooled Resource Open-Access ALS Clinical Trials cohort. Muscle Nerve. 2018 Jun;57(6):937-945.

298. Rooney J, Burke T, Vajda A, Heverin M, Hardiman O. What does the ALSFRS-R really measure? A longitudinal and survival analysis of functional dimension subscores in amyotrophic lateral sclerosis. J Neurol Neurosurg Psychiatry. 2017 May;88(5):381-385

299. National Institute of Health and Care Excellence. Interim methods guide: Highly Specialised technologies 2017. Available at https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-highly-specialised-technologies-guidance/HST-interim-methods-process-guide-may-17.pdf

300. Cowles E, Marsden G, Cole A, Devlin N. A Review of NICE Methods and Processes Across Health Technology Assessment Programmes: Why the Differences and What is the Impact? Appl Health Econ Health Policy. 2017 Aug;15(4):469-477
301. Fang T, Al Khleifat A, Meurgey JH, et al. Stage at which riluzole treatment prolongs survival in patients with amyotrophic lateral sclerosis: a retrospective analysis of data from a dose-ranging study. Lancet Neurol. 2018;17(5):416-422
302. Champion AR, Lewis S, Davies S, Hughes DA. Managing access to advanced therapy medicinal products: Challenges for NHS Wales. Br J Clin Pharmacol. 2020 Jun 3
303. Cappella M, Ciotti C, Cohen-Tannoudji M, Biferi MG. Gene Therapy for ALS-A Perspective. Int J Mol Sci. 2019 Sep 6;20(18):4388. doi: 10.3390/ijms20184388
304. Reed C, Barrett A, Lebrec J, et al. How useful is the EQ-5D in assessing the impact of caring for people with Alzheimer's disease?. Health Qual Life Outcomes. 2017;15(1):16
305. Brazier J, Longworth L. NICE DSU Technical Support Document 8: An Introduction to the Measurement and Valuation of Health for NICE Submissions [Internet]. London: National Institute for Health and Care Excellence (NICE); 2011 Aug
306. Wittenberg E, James LP, Prosser LA. Spillover Effects on Caregivers' and Family Members' Utility: A Systematic Review of the Literature. Pharmacoeconomics. 2019;37(4):475-499
307. NICE. Single technology appraisal: Nusinersen for treating spinal muscular atrophy TA588. Available at https://www.nice.org.uk/guidance/ta588 (accessed June 2020)
308. Thomas PT, Warrier MG, Sadasivan A, Balasubramanium B, Preethish-Kumar V, Nashi S, Polavarapu K, Krishna G, Vengalil S, Rajaram P, Nalini A. Caregiver burden and quality of life of patients with amyotrophic lateral sclerosis in India. Amyotroph Lateral Scler Frontotemporal Degener. 2018 Nov;19(7-8):606-610
309. National Institute for Health and Care Excellence. Available at https://www.nice.org.uk/news/blog/nice-to-support-new-valuation-study-for-england-for-eq-5d-5l-questionnaire (last accessed July 2020)

310. Gibbons C, Pagnini F, Friede T, Young CA. Treatment of fatigue in amyotrophic lateral sclerosis/motor neuron disease. Cochrane Database Syst Rev. 2018 Jan 2;1(1)

311. Paynter C, Cruice M, Mathers S, Gregory H, Vogel AP. Communication and cognitive impairments and health care decision making in MND: A narrative review. J Eval Clin Pract. 2019 Dec;25(6):1182-1192.

312. Canaway A, Al-Janabi H, Kinghorn P, Bailey C, Coast J. Development of a measure (ICECAP-Close Person Measure) through qualitative methods to capture the benefits of end-of-life care to those close to the dying for use in economic evaluation. Palliat Med. 2017;31(1):53-62

313. Dorst J, Chen L, Rosenbohm A, et al. Prognostic factors in ALS: a comparison between Germany and China. J Neurol. 2019 Jun;266(6):1516-1525.

314. Calvo A, Moglia C, Lunetta C, et al. Factors predicting survival in ALS: a multicenter Italian study. J Neurol. 2017 Jan;264(1):54-63.

315. Vucic S, Rutkove SB. Neurophysiological biomarkers in amyotrophic lateral sclerosis. Curr Opin Neurol. 2018 Oct;31(5):640-647

316. Miller TM, Pestronk A, David W, et al. An antisense oligonucleotide against SOD1 delivered intrathecally for patients with SOD1 familial amyotrophic lateral sclerosis: a phase 1, randomised, first-in-man study. Lancet Neurol. 2013 May;12(5):435-42.

317. Ludolph AC, Schuster J, Dorst J, et al. Safety and efficacy of rasagiline as an add-on therapy to riluzole in patients with amyotrophic lateral sclerosis: a randomised, double-blind, parallel-group, placebo-controlled, phase 2 trial. Lancet Neurol. 2018 Aug;17(8):681-688.

318. Leigh PN, Swash M, Iwasaki Y, et al. Amyotrophic lateral sclerosis: a consensus viewpoint on designing and implementing a clinical trial. Amyotroph Lateral Scler Other Motor Neuron Disord 2004;5(2):84-98.

319. Proudfoot M, Jones A, Talbot K, Al-Chalabi A, Turner MR. The ALSFRS as an outcome measure in therapeutic trials and its relationship to symptom onset. Amyotroph Lateral Scler Frontotemporal Degener. 2016 Jul-Aug;17(5-6):414-25

320. Franchignoni F, Mora G, Giordano A, et al. Evidence of multidimensionality in the ALSFRS-R Scale: a critical appraisal on its measurement properties using Rasch analysis. J Neurol Neurosurg Psychiatry 2013;84(12):1340-1345.

321. Geevasinga N, Howells J, Menon P, van den Bos M, Shibuya K, Matamala JM, Park SB, Byth K, Kiernan MC, Vucic S. Amyotrophic lateral sclerosis diagnostic index: Toward a personalized diagnosis of ALS. Neurology. 2019 Feb 5;92(6):e536-e

Appendix 1: Published version of chapter two: Moore A, Young CA, Hughes DA. Mapping ALSFRS-R and ALSUI to EQ-5D in Patients with Motor Neuron Disease

Reference: Moore A, Young CA, Hughes DA. Mapping ALSFRS-R and ALSUI to EQ-5D in Patients with Motor Neuron Disease. Value Health. 2018 Nov;21(11):1322-1329. doi: https://doi.org/10.1016/j.jval.2018.05.005

Appendix 2: Published version of chapter four: Health Utilities and Costs for Motor Neurone Disease

Reference: Moore A, Young CA, Hughes DA. Health Utilities and Costs for Motor Neurone Disease. Value Health. 2019 Nov;22(11):1257-1265. doi: https://doi.org/10.1016/j.jval.2019.05.011

Appendix 3: Search strategy chapter two systematic review

Medline Ovid Search Strategy

1. Econ*.sh
2. Economic Model.mp
3. Discrete Event Simulation.mp
4. Decision Analysis.mp
5. Markov*.mp
6. ICER or Incremental Cost Effectiveness Ratio .mp.
7. exp cost benefit/
8. exp cost analysis/
9. cost$2 adj2 (benefit$ or effect* or analy* or utility$ or minim* or utilit*) .mp.
10. Quality Adjusted Life Year$ or QALY$ .mp.
11. Life year$ gain* .mp.
12. cost*.kw.ti.ab
13. economic adj2 cost$.mp
14. Socioeconomic.mp
15. Productivity Costs or Absenteeism.mp
16. Healthcare cost$ or Cost$ of Illness.mp
17. exp cost analysis/
18. financ*.ti.ab
19. Utilit*.mp
20. HSUV or Health State Utility Values.mp
21. Standard Gamble.ti.ab
22. Time Trade Off.ti.ab
23. Visual Analogue Scale.ti.ab
24. EQ-5D.ti.ab
25. SF-36 or Short Form 36.ti.ab
26. SF6D.ti.ab
27. ALS Utility Index or Amyotrophic Lateral Sclerosis Utility Index
28. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27
29. exp Motor Neuron$ Disease
30. Amyotrophic Lateral Sclerosis.mp.
31. Lou Gehrig$ adj 2 (Disease or Syndrome).mp.

32. Progressive Muscular Atrophy.mp.
33. Progressive Bulbar Palsy.mp.
34. Primary Lateral Sclerosis.mp.
35. Charcot Disease.mp.
36. 29 or 30 or 31 or 32 or 33 or 34 or 35
37. 28 and 36
38. Comment.pt
39. Editorial.pt
40. Letter.pt
41. 38 or 39 or 40
42. 37 not 41
43. Limit 42 to English

EconLit Search Strategy

(MESH(ECON*) OR all((economic model OR discrete event simulation)) OR all((Markov* OR Incremental Cost Effectiveness Ratio)) OR all((cost benefit analysis OR cost effectiveness)) OR all((cost analysis OR cost utility)) OR all((QALY* OR quality adjusted life year*)) OR all(life year* gain*))

OR

(TI,AB(cost*) OR all((Productivity OR absenteeism)) OR all((Healthcare cost* OR Cost Analysis)) OR all((cost of illness OR Direct costs)) OR all(Indirect costs) OR TI,AB(finac*))

OR

(all(Utilit*) OR all((Health State Utility Values OR standard gamble)) OR all((time trade off OR EQ-5D)) OR all((visual analogue scale OR sf-36)) OR all((SF-6D)) OR all(ALS Utility Index))

AND all(Motor Neurone Disease) OR all((Amyotrophic Lateral Sclerosis OR Lou Gehrig* disease)) OR all((progressive muscular atrophy OR progressive bulbar palsy)) OR all((primary lateral sclerosis OR Charcot disease

Appendix 4 – Additional mapping information for chapter 3

Supplementary Table – Direct mapping model coefficients (mean, se) and performance

	Model OLS1	**Tobit 1**	**OLS 1b**	**Tobit 1b**	**OLS 2**	**Tobit 2**	**OLS 3**	**Tobit 3**	**OLS 4**
Intercept	-0.0764070 (0.0322988)	-0.092619 (0.033584)	-0.2006842 (0.0561154)	-0.201434 (0.0576542)	0.207981 (0.036821)	0.207270 (0.037773)	0.108231 (0.26880)	0.100416 (0.027468)	-0.0764070 (0.0203011)
Bulbar Domain	N/A	N/A	N/A	N/A	0.005273 (0.002425)	0.005336 (0.002484)	0.004021 (0.001936)	0.004049 (0.001969)	N/A
Fine Motor Domain	N/A	N/A	N/A	N/A	0.045773 (0.002701)	0.047382 (0.002791)	N/A	N/A	N/A
Gross Motor Domain	N/A	N/A	N/A	N/A	0.0044689 (0.002497)	0.003832 (0.002559)	N/A	N/A	N/A
Motor Domain	N/A	N/A	N/A	N/A	N/A	N/A	0.033891 (0.001165)	0.034743 (0.001206)	N/A
Respiratory Domain	N/A	N/A	N/A	N/A	-0.004918 (0.002038)	-0.009103 (0.002605)	-0.004918 (0.002547)	-0.005067 (0.002066)	N/A
ALSFRS-R Index Score	0.0203011 (0.009782)	0.020893 (0.001021)	0.0210841 (0.0009069)	0.0232141 (0.0011245)	N/A	N/A	N/A	N/A	N/A
ALS Utility Index	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	0.6453 (0.03658)
Age	N/A	N/A	0.0004728 (0.007009)	0.0004728 (0.007009)	N/A	N/A	N/A	N/A	N/A
Gender (Male = 1)	N/A	N/A	0.0306621 (0.0156760)	0.0315324 (0.0163413)	N/A	N/A	N/A	N/A	N/A
Bulbar onset (dummy variable)	N/A	N/A	0.1801147 (0.0174122)	0.1813274 (0.0182437)	N/A	N/A	N/A	N/A	N/A
Respiratory Onset (dummy	N/A	N/A	0.0841561 (0.0560579)	0.0856382 (0.0572295)	N/A	N/A	N/A	N/A	N/A

variable)									
EQ-5D <0 MSE (MAE)	0.1984 (0.4050)	0.2001 (0.4071)	0.0216 (0.4085)	0.0211 (0.4097)	0.2090 (0.4120)	0.2101 (0.4132)	0.1473 (0.3402)	0.1481 (0.3502)	0.2017 (0.3401)
EQ-5D 0-0.2 MSE (MAE)	0.1005 (0.2710)	0.1023 (0.2781)	0.0985 (0.2083)	0.0995 (0.2120)	0.1085 (0.2148)	0.1098 (0.2165)	0.0782 (0.2334)	0.0791 (0.2350)	0.1152 (0.2541)
EQ-5D 0.2-0.4 MSE (MAE)	0.0447 (0.1794)	0.04558 (0.1835)	0.0373 (0.1557)	0.0387 (0.1569)	0.0460 (0.1882)	0.0480 (0.1980)	0.0337 (0.1498)	0.0375 (0.1504)	0.0414 (0.1453)
EQ-5D 0.4-0.6 MSE (MAE)	0.0217 (0.1204)	0.0231 (0.1245)	0.0299 (0.1204)	0.0321 (0.1250)	0.0245 (0.1380)	0.0256 (0.1395)	0.0195 (0.0975)	0.0203 (0.0105)	0.0257 (0.1292)
EQ-5D 0.6-0.8 MSE (MAE)	0.0201 (0.1109)	0.0212 (0.1189)	0.0189 (0.1107)	0.0198 (0.1125)	0.0210 (0.1190)	0.0235 (0.1205)	0.0145 (0.0979)	0.0154 (0.1023)	0.0214 (0.1278)
EQ-5D 0.8-1 MSE (MAE)	0.0415 (0.1535)	0.0456 (0.1565)	0.0415 (0.1764)	0.0405 (0.1769)	0.0405 (0.1523)	0.0412 (0.1542)	0.0226 (0.1217)	0.0247 (0.1240)	0.0315 (0.1452)
Absolute differences >0.1	36.9%	37.3%	42.2%	41.5%	34.1%	33.2%	44.2%	43.7%	29.8%
Absolute differences >0.25	83.3%	81.2%	83.8%	82.3%	75.3%	74.5%	85.7%	84.7%	79.7%
Adjusted R^2	0.42	0.41	0.51	0.49	0.38	0.36	0.60	0.61	0.34

Supplementary Table 2b – Direct mapping model coefficients (mean, se) and performance

	Tobit 4	**OLS 5**	**Tobit 5**	**OLS 6**	**Tobit 6**
Intercept	0.030722 (0.01768)	0.1357405 (0.0376646)	0.1306621 (0.0379104)	0.086203 (0.022151)	0.078211 (0.22554)
Item 1	N/A	- 0.0009210 (0.0080445)	-0.0023325 (0.0081075)	N/A	N/A
Item 2	N/A	- 0.0020943 (0.0071271)	-00035270 (0.0071868)	N/A	N/A
Item 3	N/A	- 0.0025923 (0.0086630)	-0.004861 (0.0087302)	N/A	N/A
Item 4	N/A	- 0.0079483 (0.0075627)	-0.0068227 (0.0075926)	N/A	N/A
Item 5	N/A	0.0038660 (0.0075627)	0.0037250 (0.0078988)	N/A	N/A
Item 6	N/A	0.0591589 (0.0091495)	0.0600117 (0.0091870)	0.057486 (0.007728)	0.059073 (0.0091870)
Item 7	N/A	0.0476589 (0.0087734)	0.0473987 (0.0087976)	0.046674 (0.008277)	0.0473987 (0.0087976)
Item 8	N/A	0.0596126 (0.0092378)	0.0613966 (0.0092895)	0.058688 (0.009049)	0.060471 (0.009153)
Item 9	N/A	0.0349047 (0.0073587)	0.0362611 (0.0073883)	0.035927 (0.007281)	0.037251 (0.007355)
Item 10	N/A	0.0222083 (0.0072210)	0.0234802 (0.0072606)	0.021126 (0.005736)	0.021945 (0.005797)
Item 11	N/A	0.0079571 (0.0082835)	0.0078683 (0.0083270)	N/A	N/A
Item 12	N/A	-0.0153849 (0.0121983)	-0.0164486 (0.0122450)	N/A	N/A
EQ-5D <0 MSE (MAE)	0.2061 (0.3517)	0.1169 (0.3033)	0.1189 (0.3101)	0.1187 (0.3076)	0.1191 (0.3087)
EQ-5D 0-0.2 MSE (MAE)	0.1161 (0.2561)	0.0571 (0.1998)	0.0617 (0.2001)	0.058 (0.1998)	0.0591 (0.2010)
EQ-5D 0.2-0.4 MSE (MAE)	0.0456 (0.1453)	0.0248 (0.1205)	0.0251 (0.1324)	0.0258 (0.125)	0.0261 (0.1261)
EQ-5D 0.4-0.6 MSE (MAE)	0.0257 (0.1292)	0.0125 (0.0892)	0.0122 (0.0882)	0.0127 (0.0891)	0.0124 (0.0918)
EQ-5D 0.6-0.8 MSE (MAE)	0.0192 (0.1278)	0.0171 (0.1095)	0.0181 (0.1101)	0.0167 (0.1045)	0.0171 (0.1052)
EQ-5D 0.8-1 MSE (MAE)	0.0310 (0.1478)	0.0178 (0.1001)	0.0179 (0.1012)	0.0172 (0.1014)	0.0182 (0.1019)
Absolute differences >0.1	30.30%	53.54%	53.12%	55.40%	54.52%
Absolute differences >0.25	76.26%	89.90%	89.90%	90.40%	89.38%
Adjusted R^2	0.33	0.66	0.65	0.66	0.66

Supplementary Table 3 – Indirect mapping (model 13)

	Mlogit 13	
EQ-5D Domain	Intercept	ALSFRS-R (Index)
Mobility		
Level 2	6.439424 (1.187401)	-0.1778716 (0.03130894)
Level 3	8.238533 (1.110420)	-0.2113584 (0.02910124)
Level 4	10.317563 (1.121826)	-0.2778752 (0.03017539)
Level 5	12.870616 (1.175884)	-0.3861677 (0.03295915)
Self-care		
Level 2	4.205394 (0.9367229)	-0.1065379 (0.02482013)
Level 3	7.965957 (0.9575464)	-0.2164520 (0.02617559)
Level 4	9.152800 (1.0592660)	-0.2834232 (0.03058252)
Level 5	13.084282 (1.0979207)	-0.4316174 (0.03437562)
Usual Activities		
Level 2	5.630141 (1.450577)	-0.1255271 (0.03673929)
Level 3	9.783490 (1.430415)	-0.2323781 (0.03660618)
Level 4	11.379421 (1.464921)	-0.2950725 (0.03812518)
Level 5	14.017239 (1.478238)	-0.3870526 (0.3924239)
	Intercept	Neuropathic Pain Scale
Pain		
Level 2	-1.067093 (0.3534914)	0.1070301 (0.01877203)
Level 3	-3.282011 (0.4679960)	0.1780191 (0.02537707)
Level 4	-6.997961 (0.8132573)	0.2315875 (0.02537707)
Level 5	-16.348612 (3.5069654)	0.1070301 (0.01877203)
	Intercept	MND-HADS
Anxiety/ Depression		
Level 2	-1.954728 (0.2173800)	0.2589150 (0.02930225)
Level 3	-4.864620 (0.4011287)	0.4625180 (0.04009279)

Level 4	-10.736994 (1.1774330)	0.7313353 (0.07299859)
Level 5	-11.386918 (1.709959)	0.7046343 (0.09798552)
Absolute Differences >0.1	40.32%	
Absolute Differences >0.25	76.25%	
Adjusted R^2	0.42	
Errors by EQ-5D range MSE (MAE)		
<0	0.1971 (0.3812)	
0-0.2	0.0988 (0.2617)	
0.2-0.4	0.0411 (0.1722)	
0.4-0.6	0.0262 (0.1176)	
0.6-0.8	0.0181 (0.1086)	
0.8-1	0.0321 (0.1491)	

Note: Only the best indirect model (Mlogit 13) is shown for brevity.

Supplementary Table 4 – Logistic regression results for section 3.1

Variable	**Coefficient Estimate**	**P value**
Intercept	21.66	0.998
Completed by patient (yes = 1)	-0.1828	0.637
Gender (male = 1)	-0.3082	0.412
Age	-0.0205	0.259
Bulbar Onset (Dummy coded)	-0.3271	0.395
Respiratory Onset (Dummy coded)	16.04	0.996
AB MND Centre	-0.4429	1.00
LP MND Centre	-17.37	0.999
NE MND Centre	-0.2994	1.00
NO MND Centre	-0.3725	1.00
PR MND Centre	-16.49	0.999
SF MND Centre	-17.21	0.999
SO MND Centre	-18.24	0.999
SR MND Centre	-17.65	0.999
OR MND Centre	-17.39	0.999
KC MND Centre	-17.44	0.999
EX MND Centre	-0.2911	1.00
ND MND Centre	-0.6804	1.00
PL MND Centre	-0.529	1.00
CB MND Centre	-0.557	1.00
PO MND Centre	-0.4024	1.00
YK MND Centre	-0.3701	1.00
WS MND Centre	-18.27	0.999
DV MND Centre	0.0996	1.00
SS MND Centre	-17.43	0.999
RI MND Centre	-0.3525	1.00
RF MND Centre	0.2655	1.00
QE MND Centre	-0.5262	1.00

*dependent variable = Completed Questionnaire (=1)

Appendix 5 - Supplementary appendices for chapter 4 – Cost sources and overlap of Kings and MiToS staging systems

Table 1 Unit costs for resources

Item	**Cost (£) 2017 (*inflated)**	**Source**
Hospital casualty department	137	NHS reference costs 2017
Practice Nurse, GP Surgery	13.51	Curtis 2017
Doctor, GP Surgery	37	Curtis 2017
Nurse, home visit	43.89*	Curtis and Burns 2010
Doctor, home visit	135.06*	Curtis and Burns 2010
Nurse, outpatient	119	NHS reference costs 2017
Doctor, outpatient	171.98	NHS reference costs 2017
Inpatient stay (MND spell)	2840	NHS reference costs 2017
Ambulance use	247	NHS reference costs 2017
Blood test	3	NHS reference costs 2017
Urine test	4.59*	NHS supply chain 2014
Ultrasound	55	NHS reference costs 2017
X-ray	33.32	NHS reference costs 2017
CT scan	123	NHS reference costs 2017
MRI brain scan	147	NHS reference costs 2017
EMG	200	NHS reference costs 2017
Health visitor	76.46	NHS reference costs 2017
Social worker	79	Curtis 2017
Physiotherapist	55	NHS reference costs 2017
Psychologist	53.95	Curtis 2017
Counsellor	69.91	Curtis 2017

Table 2 Concordance between Kings and MiToS staging

Number of patients for combinations of Kings and MiToS stages

Kings / MiToS	1	2	3	4
0	76	90	116	16
1	13	42	78	65
2	0	4	11	59
3	0	0	1	17
4	0	0	0	5

EQ-5D-5L Index values for combinations of Kings and MiToS stages, mean (SD)

Kings / MiToS	1	2	3	4
0	0.80 (0.18)	0.70 (0.19)	0.65 (0.18)	0.67 (0.23)
1	0.48 (0.16)	0.40 (0.21)	0.39 (0.21)	0.62 (0.25)
2	NA	0.34 (0.32)	0.28 (0.14)	0.38 (0.25)
3	NA	NA	0.30 (NA)	0.33 (0.24)
4	NA	NA	NA	0.25 (0.23)

Table 3 Resource use, costs and characteristics by MND onset type

Resource Category	Limb Onset	Bulbar Onset	Respiratory Onset
Primary Care	**Mean (Max value), all minimum values = 0**		
Nurse GP Surgery	0.37 (10)	0.73 (20)	0.36 (2)
Doctor GP Surgery	0.75 (10)	1.32 (10)	0.55 (4)
Nurse at Home	1.75 (90)	2.50 (90)	3.09 (10)
Doctor at Home	0.27 (12)	0.33 (10)	0.27 (2)
Secondary Care			
Casualty Department	0.18 (10)	0.37 (8)	0.27 (2)
Nurse Outpatient	0.81 (10)	1.47 (18)	0.91 (3)
Doctor Outpatient	2.29 (31)	1.88 (12)	1.82 (3)
Ambulance Use	0.28 (12)	0.17 (6)	0.55 (3)
Inpatient Stays	0.21 (12)	0.29 (5)	0.09 (1)
Tests			
Blood	1.14 (40)	1.12 (12)	1.27 (5)
Urine	0.09 (4)	0.16 (5)	0 (0)
Ultrasound	0.06 (3)	0.07 (2)	0 (0)
X-ray	0.17 (6)	0.24 (3)	0.09 (1)
CT Scan	0.07 (2)	0.25 (10)	0.09 (1)
MRI Scan	0.20 (6)	0.22 (2)	0.09 (1)
EMG Scan	0.25 (3)	0.32 (3)	0.18 (1)
Community Care			
Health Visitor	0.65 (46)	1.33 (20)	1 (11)
Social Worker	0.40 (10)	0.45 (14)	0.36 (2)
Physiotherapist	2.18 (40)	1.96 (20)	3.09 (9)
Psychologist	0.14 (10)	0.09 (3)	0 (0)
Counsellor	0.09 (4)	0.07 (8)	0.64 (7)
Direct costs (NHS) – 3 months	**Mean (95% CI)**		
Primary care	145 (107,181)	213 (139,287)	198 (55,341)
Secondary care	984 (644,1336)	1366 (899,1850)	724 (282,1572)
*Of which are inpatient stay costs	596 (308,894)	824 (463,1200)	256 (0,736)
Tests	101 (80,122)	143 (103,183)	68 (0,147)
Community care	241 (205,277)	382 (228,544)	349 (0,709)
Medicines	102 (85,119)	325 (197,453)	146 (0,302)
Total	1593 (1240,1940	2350 (1840,2860)	1613 (383,2840)
Characteristics	**Mean (SD) (95% CI)**		
EQ-5D-5L	0.53 (0.24) (0.49,0.57)	0.68 (0.26) (0.64,0.72)	0.53 (0.32) (0.35,0.71)
ALS Index	32.64 (7.98) (31.32, 33.24)	30.92 (8.50) (29.87,32.14)	27.91 (7.34) (23.45,31.12)
Bulbar Domain	9.85 (2.52) (9.11,10.68)	4.88 (3.08) (4.12,5.68)	10.45 (2.54) (9.86,11.12)
Gross Motor Domain	12.78 (5.41) (11.96,13.72)	16.19 (5.90) (15.56,16.89)	11.65 (7.98) (11.09,12.18)
Respiratory Domain	10.02 (2.70)	9.76 (2.28)	5.82 (3.84)

	(9.54,10.86)	(9.12,10.34)	(4.86,6.88)
ALS Utility Index	0.43 (0.28) (0.41,0.45)	0.35 (0.23) (0.32,0.38)	0.26 (0.16) (0.18,0.36)
EQ-5D VAS	59 (21) (56,62)	62 (22) (60,64)	58 (24) (48,69)

Appendix 6 – CHEERs Checklist for chapter five: Health economic evaluation of edaravone compared to standard care for the treatment of MND

Section/item	Item No	Recommendation	Reported on page No/ line No
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	Page 103
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	Page 103
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study.	Section 5.1 page 106
		Present the study question and its relevance for health policy or practice decisions.	Section 5.1 page 106
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	Section 5.2 page 109
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	Stated in title and introduction section 5.1 page 105
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	Section 5.2 page 106
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	Section 5.2 page 106
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	Section 5.2 page 109
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	Section 5.2 page 109
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	Section 5.2 page 109
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	Described in section 5.1 page 105
	11b	*Synthesis-based estimates*: Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	N/A
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	Section 5.2 page 109
Estimating resources and costs	13a	*Single study-based economic evaluation:*Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit	N/A

Section/item	Item No	Recommendation	Reported on page No/ line No
		cost. Describe any adjustments made to approximate to opportunity costs.	
	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	Described in section 5.2 page 109
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	Reported in table 5.3 page 113
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	Reported in section 5.2. page Figure 5.1 shows model structure. Page 108
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	Page 112
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	Reported throughout section 5.2 page 105 onwards.
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	Input values and transition matrix is shown in tables 5.3 and 5.4
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	ICERs Reported on page 113 onwards for base case and sensitivity and scenario analysis
Characterising uncertainty	20a	*Single study-based economic evaluation:*Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	N/A
	20b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	Various assumptions, and their effect on the ICER, is described in section 5.3.3 page 115
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be	Scenario analysis results provided in section 5.3.3

Section/item	Item No	Recommendation	Reported on page No/ line No
		explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	page 115
Discussion			
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	Discussion – section 5.4 page 121
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	Information provided at begining of the thesis. Funding for thesis from Motor Neurone Disease Assocation
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	Article not yet sent to Journal – none of the authors have conflicts to declear