The clinical effectiveness and cost-effectiveness of riluzole for motor neurone disease

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Antony Stewart was the main author. He designed the protocol and piloted and modified the forms used for assessment of eligibility, validity and data extraction. He undertook searches for studies and requested further information from authors. He liaised with content experts in the field to obtain background information and support. He assessed studies for eligibility, validity and extracted data from them. He collated the data and wrote the report.

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Stirling Bryan provided health economics advice, and carried out economic modelling. He contributed to the health economics section. He read and commented on the draft report.

Chris Hyde advised on the protocol for the review and contributed to the discussion and conclusions section. He read and commented on the draft report.

Anne Fry-Smith advised on the search strategy. She read and commented on the draft report.

CONFLICTS OF INTEREST

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This report was commissioned by the NHS R&D HTA programme.

Relationship of reviewers with sponsor
Antony Stewart, Amanda Burls, Chris Hyde, Anne Fry-Smith, Josie Sandercock and Stirling Bryan have no pecuniary relationship with companies making or promoting the use of riluzole.

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Dr Keith Wheatley commented on draft versions of the report.

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ABBREVIATIONS

ALAT	Alanine aminotransferase
ALS	Amyotrophic lateral sclerosis
ALSFRS	ALS functional rating scale
ASAT	Aspartame aminotransferase
BD, BID	Twice a day
BDNF	Brain derived neurotrophic factor
CBA	Cost-benefit analysis
CEA	Cost-effectiveness analysis
CIs	Confidence intervals (95%)
CUA	Cost-utility analysis
DARE	Database of Abstracts of Reviews of Effectiveness
ECG	Electrocardiogram
EMEA	European Medicines Evaluation Agency
EQ-5D	EuroQol quality of life measurement instrument
FVC	Forced vital capacity
GOT	Glutamic-oxaloacetic transaminase
GPT	Glutamic-pyruvic transaminase
HR	Hazard ratio
HTA	Health Technology Assessment (also The NHS Health Technology Assessment database)
ICER	Incremental cost-effectiveness ratio
ITT	Intention to treat
MND	Motor neurone disease
MVIC	Maximal voluntary isometric contraction
NHS EED	NHS Economic Evaluations Database
NICE	National Institute for Clinical Excellence
OD	Once a day
OR	Odds ratio
QALY	Quality adjusted life year, used in cost-utility analysis
QD, QDS	Four times a day
RCT	Randomised controlled trial
RBC	Red blood cell count
SD	Standard deviation
SEM	Standard error of the mean
SF12	Quality of life questionnaire (SF = short form; number denotes number of questions asked)
SIP	Sickness Impact Profile
SPC	Summary of product characteristics
TMS	Transcranial magnetic stimulation
VAS	Visual analogue scale

GLOSSARY

Amyotrophic lateral sclerosis	Is the commonest sort of motor neurone disease and affects both upper and lower motor neurones. It is characterised by muscle weakness, atrophy, spasticity, brisk reflexes, emotional lability, fasciculation and weight loss.
Asthenia	Subjective sensation of weakness.
Bulbar muscles	The bulbar muscles are those muscles innervated by nerves originating in the bulbar region of the brain. They control the tongue, speech and swallowing.
Cost-benefit analysis Cost-effectiveness analysis	Attempts to measure all the resource implications and consequences in the same units (usually monetary), to demonstrate whether an intervention is worthwhile. Uses a clinical endpoint as a primary measure of outcome. Presents costs and effects for this outcome measure, usually as a cost per adverse clinical event avoided.
Cost-utility analysis	Evaluates the relative importance of each outcome in terms of improvements in length of life and health-related quality of life, expressed as a single measure such as cost per QALY.
Cox (Proportional Hazards) Model	A regression model for use with survival data. May be used to construct prognostic indices or produce adjusted analyses. The proportional hazards assumption requires that the relative treatment effect (hazard ratio) remains constant over time.
Hazard ratio	Summarises the difference between two Kaplan-Meier survival curves. May be thought of as the overall relative risk of experiencing a critical 'event' (such as death) over the period of follow-up.
Kaplan-Meier survival curves	Graphical summary of the observed survival of one or more groups of patients. Based on non-parametric estimates of survival probabilities at each time point during follow-up.
Lower motor neurone	Lower motor neurones originate in the brain stem or the anterior horn cells of the spinal cord and innervate muscle. Lesions of lower motor neurones cause characteristic signs: muscle atrophy, fasciculation, flaccid weakness, diminished reflexes.
Motor neurone	A nerve cell originating in the brain, brain stem or spinal cord through which movement is initiated or controlled.
Motor neurone disease	This term is used in two ways generically to cover all diseases that are characterised by degeneration of the motor neurones or to refer to amyotrophic lateral sclerosis.
Sensitivity analysis	Investigates how conclusions change when one or more of the inputs varies. It assesses how robust conclusions are to uncertainties, such as varying drug costs or survival.
Upper motor neurone	Upper motor neurones originate in the brain (cortico-spinal tract cells). Lesions in upper motor neurones cause characteristic signs: spasticity, stiffness, brisk reflexes, abnormal reflexes (e.g. Babinski reflex), spastic weakness.

SUMMARY

Technology evaluated

Riluzole (trade name Rilutek®) is a drug used to treat people with motor neurone disease (MND), in particular amyotrophic lateral sclerosis (ALS). Its licensed indication is to thus extend life or the time to mechanical ventilation. It costs around £3,700 per year.

Background

ALS is a progressive disorder that causes degeneration of the motor neurones of the brain and spinal cord. Symptoms include spasticity, muscle weakness and paralysis, impaired speaking, swallowing and breathing. ALS is extremely distressing for patients and their carers. The disease is relentlessly progressive and death usually occurs within 3-5 years. Survival time is significantly reduced when the disease starts with bulbar symptoms or at an older age. Death usually occurs from respiratory infection and failure and complications of immobility. There is no cure and treatment consists mostly of symptomatic, supportive and palliative care.

Epidemiology

The prevalence of motor neurone disease is around 7 per 100,000. ALS constitutes between 65-85% of this. Incidence rises with age. At any one time there are around 3,000 people in the UK with ALS. A district of 500,000 residents could expect to have around 20-25 people with ALS.

Questions addressed by the review

What is the clinical effectiveness and cost-effectiveness of riluzole for the treatment of motor neurone disease?

Methods

A systematic review of randomised controlled trials (RCTs) and economic studies addressing the above questions was undertaken and a model of the cost-effectiveness developed.

Results

RCTs found

Four studies met the inclusion criteria for the clinical effectiveness review. All compared riluzole to placebo. Three trials used riluzole at 100mg/day and one used doses of 50, 100 and 200mg/day. Three of the trials had broadly similar eligibility criteria. The fourth trial used patients who were older and more ill, with a FVC <60%. All trials had tracheostomy-free survival as a primary outcome. Most patients were prevalent, rather than incident cases, in all four trials.

Evidence on effectiveness

Combined results for three trials where full data was available favoured riluzole with a hazard ratio for tracheostomy-free survival (over a follow-up period of around 18 months) of 0.83 (95% CI 0.69-0.99). There was no statistically significant heterogeneity between the results of these trials. There was no evidence that the effectiveness of the treatment differed by site of onset. No significant difference in effectiveness in daily doses of between 50 and 200mg was found.

Riluzole does not improve symptoms. When data on functional status were combined, a small reduction in the rate of deterioration of functional status was observed, though it was not clear whether this was clinically significant. A large proportion of patients in both groups reported adverse events but there was little overall difference between riluzole and placebo. There was no evidence available about longer term treatment outcomes, beyond 18 months.

Costs and economic analysis

The evidence suggests that current estimates of the cost-effectiveness of riluzole must be viewed cautiously. Some of the key remaining uncertainties on benefits for the economic analysis concern the disease stage(s) in which any survival gain is experienced, the quality of life utility weights for ALS health states, and the mean gain in life expectancy for patients who take riluzole. Published estimates on increased life expectancy range from 2 months to 12 months. It is clear that riluzole is associated with a net increase in costs to the health service, though the magnitude of the increase is difficult to predict accurately.

A more robust estimate of the riluzole-induced gain in life expectancy over the whole duration of the disease is required to reduce current uncertainties relating to methods of extrapolating beyond observed survival in trials. Base-case ICER (incremental cost-effectiveness ratio) produced a cost per life-year of £39,000 and a cost per QALY of £58,000. A sensitivity analysis indicates that the most optimistic ICER (cost per QALY) is £20,000 and the most pessimistic has riluzole dominated by placebo.

Conclusions

There is limited evidence of a modest benefit in tracheostomy-free survival for patients taking riluzole. However, the evidence base is restricted and there remains uncertainty as to the true benefit of riluzole; the confidence interval is wide and compatible with little or no difference between riluzole and placebo. When costs and health economic impact extrapolating survival beyond that observed in trials are considered, the uncertainty about whether the benefits are worth the costs is magnified. Even under the most optimistic assumptions, riluzole at best only postpones death for a few months, and does not preclude the need for supportive care and practical help.

Consequently, existing evidence on effectiveness and cost-effectiveness does not unequivocally indicate the best policy concerning use of riluzole in ALS for the NHS.

If riluzole were to be made available to all patients in whom it is not contraindicated, the annual cost to the NHS would be around £8.4 million. This assumes all these patients wish to take it. Many patients, given accurate information about the benefits and effects of riluzole, may choose not to. Patients should be made aware that riluzole does not cure ALS, or improve quality of life. Accurate patient information is essential.

Ideally, further reliable evidence from trials is necessary to answer the many uncertainties that exist. These should include a substantial incident population, with long-term (5 year) survival follow-up, and collect health economic and quality of life data. Existing analyses not available to us and information from ALS databases may provide additional useful data in the short term.

1 AIM OF THE REVIEW

To find and examine existing evidence, in order to evaluate the effectiveness and evaluate the cost-effectiveness of riluzole in the treatment of Motor Neurone Disease (MND).

2 BACKGROUND

- Motor neurone disease (MND) is a disorder characterised by degeneration of the motor neurones of the brain and spinal cord
- Symptoms include spasticity, weakness, paralysis and impairment of speech, swallowing and breathing
- MND is a rare disease with a prevalence of around 7/100,000
- The commonest form of MND is amyotrophic lateral sclerosis (ALS), accounting for 65-85% of all cases
- At any one time, there are around 3,000 people with diagnosed ALS in the UK
- There is no cure for ALS – it is relentlessly progressive and death usually occurs within 3-5 years
- Diagnosis can take more than 16 months from symptom onset

2.1 Nature of Motor Neurone Disease

Motor neurone disease (MND) is characterised by progressive degeneration of the motor neurones of the brain, brain stem or spinal cord. It can affect both upper and lower motor neurones. Upper motor neurones (cortico-spinal tract cells) originate in the brain. Lesions in upper motor neurones cause characteristic signs such as spasticity, muscle stiffness, brisk reflexes, abnormal reflexes (e.g. Babinski reflex) and spastic weakness.

Lower motor neurones originate in the brain stem or the anterior horn cells of the spinal cord and innervate muscle. Lesions of lower motor neurones cause characteristic signs such as muscle wasting, muscle fasciculation, flaccid weakness, hypertonia and diminished reflexes.

The classification and terminology used to describe the different motor neurone diseases is not always clear or consistent. This confusion partly reflects our ignorance of the underlying causes and mechanism of neuronal damage. There is also debate as to the extent to which different syndromes are simply manifestations of the same disease process and indeed whether there are several different disease mechanisms underlying what phenomenologically appears to be the same disease.

Motor Neurone Diseases

Idiopathic motor neurone diseases
Amyotrophic lateral sclerosis (ALS)
Progressive bulbar palsy (PBP)
Progressive muscular atrophy (PMA)
Primary lateral sclerosis (PLS)
Familial ALS
Juvenile ALS
Madras motor neruone disease
Monomelic motor neurone disease

Toxin-related MNDs
Lathyrism
Konzo
Guamanian ALS

Classifications from Swash (2000)[1]

Amyotrophic lateral sclerosis (ALS) is the commonest form of MND, accounting for between 65% - 85% of all cases of MND.[1] Riluzole is licensed for the treatment of ALS, not for other variants of MND.

ALS is characterised by both upper and lower motor neurone signs. Adult-onset ALS usually starts insidiously with symptoms and signs including stumbling, foot drop, weakened grip, slurred speech, cramp, muscle wasting, twitching and tiredness.[1,2] Other symptoms of MND include muscle stiffness, paralysis, incoordination and impaired speaking, swallowing and breathing.[3]

Following the onset of clinical symptoms, ALS progresses relentlessly. Affected patients usually develop a combination of upper and lower motor neurone signs without sensory involvement, with progressive muscle weakness and wasting usually accompanied by brisk reflexes. The disease can begin in either the bulbar muscles (those involving speaking and swallowing mechanisms) or the spinal muscles (involving the limbs), though both will eventually be involved.[4] Memory, intellect, sensation, external ocular muscles and sphincters are not normally impaired.[5]

There is no diagnostic test for ALS. Clinical evaluation and investigation is essential[6] as conditions (some of which are potentially treatable) such as thyrotoxicosis, tumours, Lyme disease, poisoning by toxins such as lead or mercury, post-polio syndrome, diabetic amyotrophy, monomelic amyotrophy and post-radiation myeloplexopathy can mimic ALS.[1,7] Diagnosis is often delayed,[8] and can take more than 16 months from the onset of symptoms.[9] An internationally agreed set of criteria for diagnosing MND exists, often referred to as the El Escorial criteria.[10] A definitive staging system has not yet been developed, however.[11]
MND is extremely distressing for patients, and their increasing disability places substantial demands on carers and family members. Over half of a sample of patients with ALS in a US survey said that they would consider assisted suicide.[12] The disease is usually fatal within 3-5 years from the onset of symptoms.[4,5] Survival time is significantly reduced in bulbar onset [13,14] and onset in older age.[15,16] For patients with bulbar onset, median survival time is approximately 2 years, with 5% survival to 5 years. Patients with spinal onset survive for a median of approximately 2.5 years, with 15% survival to 5 years. Death usually occurs from respiratory infection and failure,[17] and complications of immobility.[5] Symptoms can be controlled so that death can be peaceful.[18,19]

No treatment has previously been shown to substantially alter the progression of motor neurone disease,[5] though it has been suggested that riluzole (trade name Rilutek®) may extend survival or time to mechanical ventilation in patients with ALS.

2.2 Epidemiology

2.2.1 Incidence and prevalence

Motor neurone disease is rare, with an overall prevalence of around 7 in 100,000.[2] Incidence rises with age and this is estimated at approximately 1-2 per 100,000 per annum overall,[2,4,20] increasing to 10 in 100,000 in people aged 65-85.[7] It is estimated that there are around 3,000 people with a diagnosis of ALS at any one time, in the UK, with a prevalence of between 4-5 per 100,000.[21] A district of 500,000 residents could therefore expect to have around 20-25 people with ALS.

World-wide, MND affects around 350,000 people, and nearly 120,000 new cases are diagnosed each year.[3] The age of onset is usually after 50 years of age, and very uncommon before 30. Prevalence is higher in males,[5] with a male/female ratio of 3:2.[2] It has been estimated that the average UK general practitioner will encounter only one new patient with ALS every 20-25 years.[8] African-Caribbean subjects appear more likely to have upper limb onset, and may experience a shorter survival time.[22]

2.2.2 Hospital activity

There were 1,961 hospital admissions for MND in England during 1997/8, giving an admission rate of 4 per 100,000.[23]

2.2.3 Aetiology

While the aetiology is unknown, it is thought that excessive stimulation or toxic activation of glutamate receptors on neurones may play an important role in causing the disease.[4,24] Other possible (though unproven) causes include viral infection, toxins, trauma, excessive formation of free radicals and electric shock.[2,5] A study of mortality rates from motor neurone disease has shown an excess of deaths in leather workers.[25] Five percent of cases are familial, around one-fifth of which result from a genetic defect on chromosome 21.[2]

2.3 Description of technology

- Riluzole is a drug licensed to treat people with ALS; it is not licensed for any other form of MND
- It does not cure the disease or improve symptoms but is claimed to prolong survival
- Riluzole is thought to protect cells from glutamate mediated damage
- It is the only drug currently licensed for treating ALS
- Recorded side effects include abnormal liver function, nausea and weakness
- Riluzole costs around £3,700 per year at the current recommended dose of 100mg/day (50mg bd)

Riluzole (trade name Rilutek®) is manufactured by Rhône-Poulenc Rorer (now part of Aventis Pharma). It is classified as a prescription only medicine (POM), and is presented in film -coated tablet form for oral administration. Originally developed as an anticonvulsant,[26] it was launched in August 1996 as "the first anti-excitotoxic agent proven to extend life in amyotrophic lateral sclerosis".[27]

2.4 Mechanism of action

It is hypothesised that excessive stimulation of glutamate receptors on neurones may cause or play an important role in the destruction of motor neurones in MND.[4] Glutamate is a neurotransmitter that tends to excite motor neurone cells. In vitro, riluzole inhibits the release of glutamate, decreases firing of motor neurones induced by glutamate receptor agonists and thus protects cells from glutamate-mediated damage.[27] In vivo, it has neuroprotective effects, as well as anticonvulsant and sedative properties.[28] It seems to have a dual mechanism of action: it activates a G-protein-dependent process that leads both to the inhibition of glutamate release and to the blockade of some of the post-synaptic events of the NMDA receptors, e.g. the mobilisation of calcium.[29]

2.5 Licensing

Riluzole is currently the only drug licensed for treating ALS in the UK. The licensed indication of riluzole is "to extend life or the time to mechanical ventilation for patients with amyotrophic lateral sclerosis". The Summary of Product Characteristics (SPC) recommends that riluzole "should not be used in any other form of motor neurone disease. The SPC also suggests that treatment should only be initiated by specialist physicians with experience in the management of motor neurone disease.[27,30]

2.6 Adverse effects

The main caution is history of abnormal hepatic function. Regular blood testing (every month for 3 months, then every 3 months for a further 9 months and annually thereafter) is required to monitor hepatic function.[31] Side effects include nausea, vomiting, weakness, tachycardia, somnolence, headache, dizziness, vertigo, pain, parasthesia and alterations in liver function tests.[32] Side effects of dizziness or vertigo may affect performance of skilled tasks, such as driving. Riluzole is contraindicated in patients with hepatic and renal impairment, pregnancy and breast-feeding.

2.7 Cost

The recommended dosage is 50mg twice daily. Riluzole costs £286.00 per 56 50mg tablets.[30] This equates to an approximate annual cost of £3,700.

2.8 Current service provision and utilisation

- Treatment for MND consists mainly of supportive or palliative care
- Riluzole is the only treatment licensed specifically for ALS
- Ninety-two percent of Health Authorities responding to a survey (66% of all Health Authorities responded) currently permit the use of riluzole

Riluzole is the only drug currently licensed for ALS. Apart from this, only supportive and palliative care is currently available for sufferers.[33] A wide range of multidisciplinary health and social services may be required,[34] particularly in the late stages of the disease, and are tailored to suit individual needs. NHS services may include:

- Physiotherapy
- Speech therapy
- Symptomatic treatment
- Mobility aids
- Occupational therapy
- District nursing

In the late stages, the following interventions may be required:

- Enteral feeding (for severe dysphagia)
- Ventilation (non-invasive)
- Domiciliary or hospice care
- Mechanical ventilation/tracheostomy

As riluzole does not actually cure ALS, it would be adjunctive to normal palliative care.[31] Unless riluzole treatment is discontinued due to adverse events, patients will normally take the drug for the rest of their lives.

Considerable variation exists in the level of riluzole prescribing between different countries.[9,35]

Consultation with clinical experts in the UK revealed anecdotal evidence of substantial variation in prescribing policy between individual Health Authorities. A confidential survey of all Health Authorities in England, Wales and Scotland was therefore undertaken as part of this review.

A total of 80 replies were received (out of 104 Health Authorities in England & Wales, plus 15 Health Boards in Scotland), representing a response rate of 67%.

Of the responders:

- Seven (9%) prohibited the use of riluzole
- Seventeen (21%) allowed GPs to prescribe it
- Nineteen (24%) allowed GPs to prescribe it under the direction of a neurologist
- Twenty-two (28%) only allowed a neurologist to prescribe it
- Nine (11%) only allowed its use within a shared care programme
- Three (4%) had an exceptions procedure to decide on individual cases
- Three (4%) had not yet agreed a policy on riluzole prescribing

Seven Health Authorities had formulated their own guidelines on its use.

The use of riluzole was allowed by 91% of responding Health Authorities, although one third did not respond.

A total of 3,700 prescriptions for riluzole were dispensed in the community in 1998.[36] This does not reflect hospital prescribing, for which national figures are not available in the UK.

Total sales of Rilutek® were €80 million (around £50.2 million) in 1999, a 30.3% increase on the previous year.[37] The drug has been registered in over 50 countries, and given to more that 50,000 patients. The current level of annual spending on riluzole in the UK is estimated at around £2.5 million.[21]

3 REVIEW METHODS

3.1 Review questions

The following questions are addressed in this review by assessing existing evidence:

1. What is the clinical effectiveness of riluzole for the treatment of motor neurone disease?

2. What is the cost-effectiveness of riluzole for the above indication?

3.2 Steering group

The review was carried out under the guidance of a steering group comprising a lead reviewer (AS), a main editor (AB), an information scientist (AFS), a senior advisory reviewer (CH), a medical statistician (JS) and a health economist (SB).

All members of the steering group had expertise in different areas of systematic reviewing and experience in producing DES reports and other reviews. The steering group met regularly to discuss progress, review drafts and decide direction.

Additionally, an advisory group of clinical and statistical experts was contacted, to provide clinical and statistical expertise to the review. Details of this group appear at Appendix 1, on page 53.

3.3 General methods

The methods of review generally adhered to the guidance laid out in the West Midlands DES Handbook[38] and the York CRD guidelines.[39]

A protocol for the review was produced. There were no major departures from this, though the particular importance of patient perspectives became apparent, resulting in the addition of a new section on this topic.

3.4 Inclusion criteria

Study design: Randomised or quasi-randomised, controlled trials comparing riluzole with placebo or another treatment for motor neurone disease. It was decided to rely on the methodology of more robust studies such as RCTs, rather than case-series or cohort studies.

Intervention: Riluzole.

Population: People with motor neurone disease, with no restrictions on age or sex.

Outcomes: Any that provided information on the effectiveness, cost-effectiveness or safety of riluzole, or quality of life/patient satisfaction associated with its use.

Method of application: Using the above criteria, two reviewers independently made the inclusion or exclusion decisions. Disagreements were resolved by consensus. Decisions were made independently of the data abstraction and prior to the detailed scrutiny of results.

3.5 Search strategy

Papers were identified using:

(i) Electronic databases: Cochrane Library (2000 Issue 2), Medline (1966-2000), Embase (1980-2000), Science Citation Index (1981-2000), National Research Register (2000 Issue 1), NHS EED, NHS Health Technology Assessment Database, DARE, and various internet search engines. A combination of index terms and text word terms were used in the searches, including:

Antiglutamate, antiexcitotoxic, riluzole, rilutek, MND, motor neuron(e) disease, ALS, amyotrophic lateral sclerosis

Where appropriate, the strategy for identifying controlled trials recommended by the Cochrane Collaboration[40,41] was used.

(ii) Hand searching the Aventis Pharma submission to the National Institute for Clinical Excellence
(iii) Contacting clinical experts and specialist organisations (listed in Appendix 2, on page 54.)
(iv) Citation lists
(v) Conference abstracts (listed in Appendix 3, on page 55.)

Information on cost-effectiveness and quality of life was sought from Medline, NHS EED, NHS Health Technology Assessment Database, DARE, Embase and Science Citation Index.

There were no language restrictions. The searches were last carried out on 28 June 2000. Further details of the search strategy and results are available from the authors.

3.6 Quality assessment strategy

Using a structured form, two reviewers independently assessed the validity of the study design for: sample size; duration; randomisation procedure; concealment of allocation; blinding; drop-outs; losses to follow-up; intention to treat analysis used; comparability of groups at entry and performance bias. The disagreements that occurred were resolved by consensus. Study quality was assessed, and studies were also assigned a quality grade using the Jadad scale.

3.7 Data extraction strategy

Two reviewers, using a data extraction form, independently abstracted the data. Disagreements that occurred were resolved by consensus. Data were extracted on the following:

- Details of the **study population** and baseline comparability of intervention and control groups
- Details of the **intervention** such as: drug; dosage; mode of administration; duration of treatment
- Details of the **individual outcomes measured** such as: identification of all outcomes which study protocols state will be measured; the specific measurement tool or data collection method; when, how and by whom the outcome data was collected; drop-outs; cross-overs and losses to follow-up for each outcome
- Details of **the results**, where available, as raw numbers, plus any summary measures with standard deviations, p-value and confidence intervals where possible.

3.8 Methods of analysis

3.8.1 Clinical effectiveness

All trials included an endpoint of tracheostomy-free survival, i.e. time to tracheostomy or death. The inclusion of tracheostomy as well as death as an 'event' deals with the obvious problem that time of death may be strongly influenced by the use of life support.

All trials also included endpoints dealing with functional status; in particular, all trials reported changes in muscle testing scores, the Norris bulbar scale and the Norris Limb scale. Details of functional scales (reproduced from a secondary trial report by Lacomblez *et al*[42]) appear in Appendix 4, on page 56.

Tracheostomy-free survival

For survival data, the appropriate summary statistic is the hazard ratio, which summarises the overall relative risk (of experiencing a critical event) over the period of follow-up of all patients. Hazard ratios and associated confidence intervals were extracted from the trial reports, or estimated from the summary data for the Kaplan-Meier survival curves where these were not reported directly (see Appendix 7 on page 61 for details). Pooled estimates were derived using the 'fixed effects' model.

Functional status

Mean scores and standard errors for each scale were extracted from trial reports and combined using the 'fixed effects' model.

3.8.2 Economic evaluation

A critical appraisal of published economic evaluations of the use of riluzole in ALS was carried out. Given the wide variation in published cost-effectiveness estimates, an original economic evaluation was also conducted which includes both a base-case and sensitivity analysis. Full details of the methods adopted and results found are reported in Section 5 of this Report.

4 RESULTS - CLINICAL EFFECTIVENESS

4.1 Studies identified

- Four RCTs met the inclusion criteria
- All compared riluzole to placebo
- Three trials used riluzole at 100mg/day, while the other used doses of 50, 100 and 200mg/day
- Patients were mainly recruited from the prevalent (rather than incident) population
- Patients were generally similar between three of the trials; one trial recruited patients who were older and more severely ill
- All trials reported tracheostomy-free survival as a main outcome
- However, one of these trials could not be included in the meta-analysis because of the way the results had been reported

Searching yielded a total of 298 separate references, of which 231 were from electronic databases. Many individual references were identified by more than one database. The above figures exclude duplications.

Four RCTs were identified; all met the inclusion criteria for this review.[43-46] Eight further possibly eligible papers[47-54] (based on title abstract) were examined and excluded, for reasons which are explained in Section 4.1.1. None of the excluded studies were RCTs.

Three previous systematic reviews were also identified.[31,55,56] The systematic reviews are summarised at Appendix 5, on page 58.

As well as identifying studies and systematic reviews on the clinical effectiveness of riluzole, other references were found, including studies of other drugs for ALS, non-clinical effectiveness studies of riluzole, non-systematic reviews, background information on riluzole and MND, health economic studies and conference proceedings.

The health economic studies identified are discussed in Section 5.2, page 33.

We are aware of the existence of 50 month survival data for the trial by Lacomblez *et al.* Although Aventis agreed to provide this,[57] it had not been received by the submission date for this review. We are also aware that an individual patient data meta-analysis of the four RCTs that we identified has been conducted, but not published in full.

4.1.1 Excluded studies

The study by Riviere *et al* (1998)[47] re-analysed previous trial data, and was therefore excluded. Trials by Sojka *et al* (1997),[48] Kalra *et al* (1998),[49] Gawel (1999),[50] Desiato *et al* (1999)[52] and Couratier *et al* (2000)[54] were excluded because subjects were not randomised. The trials by Arrida-Mendicoa *et al* (1999)[51] and Pongratz *et al* (1999)[53] were excluded because they did not use controls.

The excluded trials are summarised at Appendix 6, on page 59.

4.1.2 Included trials

Four trials on the effectiveness of riluzole met all of the inclusion criteria. These were Bensimon *et al* (1994),[43] Lacomblez *et al* (1996),[44] Meininger *et al* (1995)[45] and Yanagisawa *et al* (1997).[46]

Authorship of each of the first three trials was very similar. This indicates the close inter-relationship between these trials.

The number of patients included in the trials totalled 1,477. These recruited mainly from the prevalent population, rather than incident. i.e. midway through the course of the disease, rather than at its outset. Of these, 503 patients were randomised to placebo and 974 to riluzole (493 at 100mg/day).

The trial by Meininger *et al*[45] is an unpublished study, and Yanagisawa *et al*[46] is in Japanese. The former was included in only one previous systematic review and the latter by none.

A meta-analysis using individual patient data from all four of these trials has been carried out by the manufacturer, and reported in a European Public Assessment Report,[58] although it is otherwise unpublished. A report of this was received after this review was completed. A copy of the report we received accompanies this document, and we have given some brief comments in Appendix 10 on page 69.

4.2 Overview of included trials

4.2.1 Interventions and comparators

Each trial compared riluzole to placebo. Three of the trials used riluzole at 100mg/day, while the fourth was a dose-ranging study, using doses of 50, 100 and 200mg/day. A summary of interventions and comparators appears within Table 1, page 18.

4.2.2 Trial characteristics

All of the four trials were RCTs. Three trials had similar inclusion and exclusion criteria; the main differences were that Bensimon *et al* and Lacomblez *et al* excluded patients with greater than 5 years prior duration of disease or FVC less than 60%, whilst Yanagisawa *et al* required an 'event-free' life expectancy of at least 6 months and excluded patients whose FVC had decreased by more than 40% during the two months prior to randomisation. The trial by Meininger *et al* was designed specifically for those patients excluded from the Lacomblez trial, which was run in parallel. Duration of follow-up varied, ranging from 16 to 21 months; all trials had a median follow-up of 18 months. All surviving patients were censored at 18 months by the Lacomblez *et al* and Meininger *et al* trials, and to end of follow-up by both Bensimon *et al* and Yanagisawa *et al*. At the end of each study, all surviving patients were switched to riluzole. Long term comparative follow-up data will thus never be available. See Table 1 below for trial characteristics.

Table 1 - Summary of trial characteristics

	Bensimon *et al* [43]	Lacomblez *et al* [44]	Meininger *et al* [45]	Yanagisawa *et al* [46]
Intervention	Riluzole 100mg/day	Riluzole 50mg/day Riluzole 100mg/day Riluzole 200mg/day	Riluzole 100mg/day	Riluzole 100mg/day
Comparator	Placebo	Placebo	Placebo	Placebo
Design	RCT	RCT	RCT	RCT
Country	France & Belgium	France, Belgium, Germany, Spain, UK, USA & Canada	France & Belgium	Japan
Number of centres	6	30	10	48
No. patients randomised	155	959	168	195
No. placebo / riluzole	78 / 77	242 / 717 Riluzole 50mg - 237 Riluzole 100mg - 236 Riluzole 200mg - 244	86 / 82	97 /98
Inclusion criteria	Outpatients age 20-70 Probable/definite ALS ≤5 years since first symptoms ≥60% predicted FVC	Age 18-75 Probable/definite ALS ≤5 years duration ≥60% predicted FVC Aspartate & alanine aminotransferases ≤ twice limit of normal range	One or more of following: Outpatients age >75 Probable/definite limb or bulbar ALS > 5 years duration <40% predicted FVC Able to understand & give informed consent Only lower motor neuron signs	Age 20-75 Probable/definite ALS FVC deterioration <40% over last 2 months Informed consent Ambulatory Able to tolerate riluzole
Exclusion criteria	Signs of conduction blocks of motor or sensory nerves Paraproteinuria Immunoelectrophoresis Substantial lesions Signs of dementia Tracheostomy Incapacity or life-threatening disease Hepatic or renal dysfunction Pregnancy	Tracheostomy Renal dysfunction Other life-threatening or incapacitating disease Pregnancy	Tracheostomy present or expected ≤2 months Signs of dementia/major psychiatric illness Serious illness/handicap ALAT or ASAT > 2x normal limits Creatinine plasma >200µm/1 Multiple conduction block On hepatoxic Drug	Serious disease affecting prognosis Need tracheostomy in next 6 months Dementia/psychiatric disorder Renal insufficiency Pregnancy GOT/GPT ≥2 x upper normal limits Conduction block Renal drugs Physicians opinion
Duration of follow-up	483-632 days (median 548)	442 - (cut-off)548 days (median 548)	cut-off 548 days (median 548)	max. 630 days (median 548)
Censored at	End of follow up	18 months	18 months	End of follow up
Reporting intervals (months)	0,3,6,9,12,15,18,21	0,3,6,9,12,15,18	0,3,6,9,12,15,18	0,3,6,9,12,15,18,21

4.2.3 Validity

All of the four trials were randomised and described as double-blind. Intention to treat analysis was used in all trials. There was clear definition of patient groups, adverse events were reported and outcomes clearly defined.

The randomisation method was described in all but one trial (Meininger *et al* ,unpublished). It was not always clear whether treatment was masked from investigators. The number of protocol violations varied widely, though none were reported by Meininger *et al*. A Jadad score was calculated for each trial. This gives an indication of a trial's quality, taking aspects of its design and reporting into account. The score ranges from 0-5, where 5 is the highest. The trial by Meininger *et al* had a Jadad score of 3, which may simply be a reflection of the format in which the data were available to us. It seems unlikely that this trial, run in parallel with and by the same investigators as Lacomblez *et al* would have been designed and conducted to a lower standard.

The majority of patients in all trials were followed for survival endpoints for a period of 18-21 months (the maximum duration of the trials) and very few were censored before 15 months. The relatively large number of patients censored before 18 months in the trial by Lacomblez *et al* was due to the fact that this trial started later in some countries, thus some patients had been randomised for less than 18 months at the time of analysis.

The validity of included trials is summarised at Table 2.

Table 2 - Validity of included trials

	Bensimon *et al* [43] n=155	**Lacomblez *et al*** [44] n=959	**Meininger *et al*** [45] n=168	**Yanagisawa *et al*** [46] n=195
Randomised?	Yes	Yes	Yes	Yes
Randomisation method described?	Yes	Yes	No	Yes
Double-blind?	Yes	Yes	Yes	Yes
Treatment masked from patients?	Yes	Yes	Yes	Yes
Treatment masked from investigators?	Unsure	Yes	Unsure	Yes
Intention to treat analysis used?	Yes	Yes	Yes	Yes
Clear definition of patient groups?	Yes	Yes	Yes	Yes
Loss to follow-up reported?	Yes	Yes	No	Yes
Adverse events reported	Yes	Yes	Yes	Yes
Outcomes clearly defined	Yes	Yes	Yes	Yes
Jadad score	4	5	3	5
Number of protocol violations - placebo - riluzole	13 11	7 28	Not reported Not reported	1 0
True loss to follow up -overall - placebo - riluzole	0 0 0	9 Not reported Not reported	Not reported	24 14 10
Number and % censored for survival - placebo - riluzole	*12 months* *18 months* 0 0 14 *(18%)* 15 *(19%)*	*12 months* *18 months* 1 *(<1%)* 81*(33%)* 5 *(<1%)* 251*(35%)* *(all riluzole doses combined)*	*12 months* *18 months* 0 1 *(1%)* 0 2 *(2%)*	*12 months* *18 months* 1 *(1%)* 22 *(23%)* 1 *(1%)* 20 *(20%)*

Censored patients were those who were known to be alive at the last point of contact

4.2.4 Patient baseline characteristics

The ratio of placebo: riluzole patients was approximately 1:1, except for the study by Lacomblez *et al*, which used three treatment arms. As would be expected, there was a slightly higher proportion of males, except in the trial by Meininger *et al.* The percentage of patients with bulbar onset was generally similar across trials, though somewhat lower in the trial by Bensimon *et al*. Differences in eligibility criteria for the Meininger study resulted in corresponding differences in predicted % FVC, age, duration of illness and weight in this trial, compared to the other three. There was also a greater difference in age between placebo and riluzole in the Meininger trial compared to the other trials. A summary of patient baseline characteristics appears at Table 3.

Table 3 - Summary of patient baseline characteristics

	Bensimon *et al* [43] n=155	**Lacomblez *et al*** [44] n=959	**Meininger *et al*** [45] n=168	**Yanagisawa *et al*** [46] n=195
No. patients randomised	155	959	168	195
No. placebo / riluzole	78 / 77	242 / 717	86 / 82	97 /98
No. male / female (% male)	91 / 64 (59%)	575 / 384 (60%)	82 / 86 (49%)	109 / 86 (56%)
% with bulbar onset	21% overall Placebo - 22% Riluzole - 19%	31% overall Placebo - not stated Riluzole - not stated	33% overall Placebo - 30% Riluzole - 35%	29% overall Placebo - 29% Riluzole - 29%
% with familial form of ALS	Not stated	4%	9%	Not stated
Mean % predicted FVC - all - placebo - riluzole	Not stated 86 (SD 18) 92 (SD 17)	88.2 (SD 18.9) 87.6 (SD 18.2) 50mg 88.6 (SD 18.9) 100mg 88.4 (SD 19.1) 200mg 88.2 (SD 19.4)	53.7 (SEM 2.0) 55.1 (SEM 2.6) 51.9 (SEM 3.1)	Only mean FVC stated - not % predicted
Mean age - all - placebo - riluzole	Not stated 58.1 (SD 11) 56.8 (SD 11)	56.7 (SD 11.0) 56.0 (SD 11.5) 50mg 57.1 (SD 10.7) 100mg 56.9 (SD 10.9) 200mg 56.8 (SD 10.8)	60.4 (SEM 1.0) 62.8 (SEM 1.4) 57.8 (SEM 1.4)	Not stated 58.4 (SD 10.1) 59.6 (SD 9.1)
Mean years duration - all - placebo - riluzole	Not stated 2.3 (SD 1.8) 2.2 (SD 1.7)	1.8 (SD 1.3) 1.8 (SD 1.4) 50mg 1.9 (SD 1.2) 100mg 1.7 (SD 1.2) 200mg 1.8 (SD 1.2)	3.6 (SEM 0.2) 3.9 (SEM 0.4) 3.4 (SEM 0.2)	Not stated 2.5 (SD 2.1) 2.1 (SD 2.0)
Mean baseline weight - all - placebo - riluzole	Not stated 65.1kg (SD 12) 66.0kg (SD 12)	67.7kg (SD 12.7) 68.1kg (SD 13.1) 50mg 67.6kg (SD 13.0) 100mg 68.1kg (SD 13.4) 200mg 67.1kg (SD 11.5)	60.8kg (SEM 1.0) 61.8kg (SEM 1.4) 59.7kg (SEM 1.4)	Not stated Not stated Not stated

4.2.5 Primary and secondary outcome measures

The common primary outcome measure was tracheostomy-free survival, defined in three trials as time to death, tracheostomy or intubation with artificial ventilation leading to tracheostomy. Secondary outcomes included muscle strength, functional status, FVC, patients' subjective assessment of fasciculations, cramps, stiffness and tiredness, clinicians global impression and adverse events.

There were differences in definition of outcome measures, between trials. For example, Bensimon *et al* included functional status as a primary outcome, whereas it was a secondary outcome in the other three trials. All trials reported tracheostomy-free survival, rather than death alone as a primary outcome, although the main end point in the trial by Yanagisawa *et al* was progression-free survival. All trials used similar definitions of tracheostomy-free survival (time to tracheostomy or death); Lacomblez *et al* and Meininger *et al* also included intubation as an 'event' , Yanagisawa *et al* included dependence on respirator whilst Bensimon *et al* used only tracheostomy or death in their definition. The fact that the trial by Yanagisawa *et al* also included other endpoints concerned with disease progression, such as tube nutrition and independent ambulation may indicate some disparity in definition, compared to the other trials. All trials appear to have used similar scales for assessing muscle strength and limb and bulbar function.

Primary and secondary outcomes are summarised at Table 4.

Table 4 - Primary and secondary outcomes

	Bensimon *et al* [43] n=155	**Lacomblez *et al*** [44] n=959	**Meininger *et al*** [45] n=168	**Yanagisawa *et al*** [46] n=195
Primary outcomes	Tracheostomy-free survival *(time to death or tracheostomy)* Changes in functional status after 12 months of treatment (Norris limb & bulbar)	Tracheostomy-free survival *(time to death or tracheostomy or intubation)*	Tracheostomy-free survival *(time to death or tracheostomy or intubation)*	Progression-free survival *(time to death, tube nutrition, dependence on respirator, loss of upper extremity function, independent ambulation, tracheostomy or dependence on respirator)* Tracheostomy-free survival *(time to death or tracheostomy or dependence on respirator)* Overall survival
Secondary outcomes	Muscle testing scores Respiratory function Clinical global impression of change scale Patient's subjective evaluations	Muscle strength Functional status (Norris limb & bulbar) Respiratory function Clinician global impression Patient's subjective evaluations	Muscle testing Functional scores (Norris limb & bulbar) Safety variables - adverse events, vital signs, ECG, physical examination, haematology, serum chemistry	Muscle strength Japanese Norris scales (limb & bulbar) Grip Back extension Pinch FVC Safety

4.3 Clinical Effectiveness

Tracheostomy-free survival

- Results for tracheostomy-free survival, by intention-to-treat, were available from three of the four trials (1282 patients of a total of 1477).
- There is some evidence of a small survival benefit in favour of riluzole, with a pooled hazard ratio of 0.83 (95% CI 0.69, 0.99).
- There is no clear evidence of statistical heterogeneity between the trials, although there is limited power to investigate this.
- There is some clinical heterogeneity, as one of the trials recruited a somewhat different patient group from the other three trials; considering only the two trials with data available and which recruited similar patient groups had no substantial influence on the overall results.
- There is no clear evidence that the treatment effect differs according to site of disease onset.
- It has been suggested that the benefit of riluzole may be confined to higher risk patients, but there is insufficient data available to examine the treatment effect according to 'risk'.
- One trial examined different doses of riluzole (50mg, 100mg, 200mg); there is no evidence of a difference in effectiveness between these three doses.

Functional status

- Data on the annual rate of deterioration in muscle testing scores, limb function and bulbar function were available from three of the four trials (1282 patients of a total of 1477).
- A small reduction in the annual rate of deterioration of functional status was observed; differences are marginally statistically significant for limb and bulbar function scales. It is not clear whether the observed differences are clinically significant.

Adverse events

- A large proportion of patients reported adverse events but there was little difference in these proportions between riluzole and placebo.
- Treatment withdrawal rates in these studies varied widely, from 6% to 25% for patients taking riluzole, although two of the studies reported quite similar withdrawal rates on placebo as compared to riluzole.

4.3.1 Tracheostomy-free survival

4.3.1.1 Definition of endpoint

Survival data is concerned with the time to the first occurrence of one or more critical events. 'Events' for tracheostomy-free survival were defined by the different authors as follows:

Bensimon: *"death (from any cause) and tracheostomy, since in the terminal stage of the disease respiratory failure leads to either event."*

Lacomblez: *"death (from any cause), tracheostomy, and intubation with artificial ventilation leading to tracheostomy."*

Meininger*: "death, tracheostomy or intubation."*

Yanagisawa: *"tracheostomy; dependent on respirator; death"*. (Note that the main endpoint for this trial was 'progression-free survival', which also included loss of independent ambulation, loss of upper extremities function and tube nutrition as 'events'; tracheostomy-free survival was included as an endpoint in this trial for the purpose of comparison with the earlier European trials (Bensimon and Lacomblez)).

4.3.1.2 Data available

The report of Yanagisawa *et al* gives no numerical data for the intention-to-treat analysis of tracheostomy-free survival. The other three trial reports all give at least one hazard ratio and an associated 95% confidence interval relating to a number of different (intention-to-treat) analyses of tracheostomy-free survival. For some analyses only a p-value was given; in all cases this was for the logrank test. The information available from the trial reports is shown in Table 5, below.

Table 5 - Tracheostomy-free survival results reported in included trials

Results reported for tracheostomy-free survival	Bensimon *et al* [43]	Lacomblez *et al* [44]	Meininger *et al* [45]	Yanagisawa *et al* [46]
all patients				
- unadjusted	p-value only	not reported	HR and CIs†	no data reported‡
- stratified by site of onset	not reported	HR and CIs	not reported§	no data reported‡
- adjusted (Cox model)	HR and CIs	HR and CIs	HR and CIs	no data reported‡
bulbar onset only				
- unadjusted	p-value only	not reported	HR and CIs	no data reported‡
- adjusted (Cox model)	not done	not done	HR and CIs	no data reported‡
limb onset only				
- unadjusted	p-value only	not reported	HR and CIs	no data reported‡*
- adjusted (Cox model)	not done	not done	HR and CIs	no data reported‡*

† not clear if main result was stratified by site or not
‡ results reported in text with no numerical information
§ not directly reported, but calculable from directly reported results given by site
* limb patients in Yanagisawa split into 'early' and 'advanced' disease

In addition each trial report gives a number of Kaplan-Meier survival curves with summary data at 3 monthly intervals. This data may be used to approximate the hazard ratio and an associated 95% confidence interval (see Appendix 7 on page 61). The information available from the papers, directly and approximated from the summary data on the survival curves, is summarised in Appendix 8 on page 63.

All trials used a dose of 100mg daily of riluzole but the Lacomblez trial also included comparisons with 50mg and 200mg. The results for each of these dose levels are summarised in Appendix 8, page 63. There is no evidence from these data of any difference in effectiveness between the different dose levels (see Appendix 9 on page 68 for discussion). We have therefore used pooled estimates for the three riluzole arms in the Lacomblez trial. The alternative would be to exclude data from the large number of patients receiving riluzole at doses other than 100mg, which would ignore a substantial proportion of the available randomised evidence (481 patients of the 1477 randomised in these trials), reducing the precision of the estimate from this trial and of the pooled estimates.

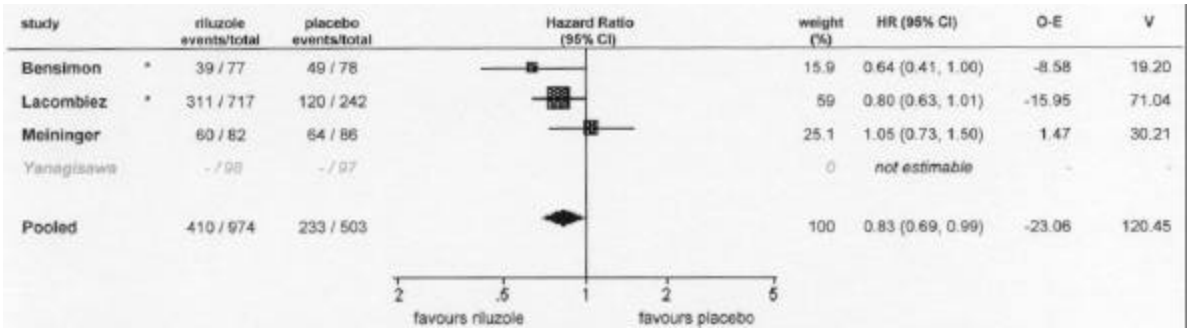
4.3.1.3 Results (tracheostomy-free survival)

No summary data for tracheostomy-free survival is available from the Yanagisawa trial. Although this endpoint was reported in the text, no numerical data or survival curves are given. The primary endpoint for this trial was progression-free survival, and survival curves are given for this endpoint (see Appendix 8, page 63). For tracheostomy free survival the authors simply note:

"There were also no significant differences between the treatment groups in this [intention-to-treat] analysis using death, tracheostomy or artificial ventilation."

The results for tracheostomy-free survival for the other three trials are summarised in Figure 1 below.

Figure 1 - Tracheostomy-free survival (unadjusted results)



*data not directly reported; results estimated using summary data from Kaplan-Meier survival curves (see Appendices 7 and 8)

There is some evidence of a modest survival benefit in favour of Riluzole. The combined hazard ratio (from the three trials where data is available) is 0.83, with a 95% confidence interval of 0.69 to 0.99. Estimates stratified by site of onset are similar to the unadjusted estimates, with an estimated hazard ratio of 0.83 and a 95% confidence interval of 0.70 to 0.98.

It is unlikely that the addition of the results from the small Yanagisawa trial would substantially alter these results. Although we were not able to obtain these data they were included in an update of a meta-analysis based on individual patient data performed by Rhone-Poulenc Rorer for the European Medicines Evaluation Agency (the other data in this meta-analysis were those from the Bensimon, Lacomblez (100mg group only) and Meininger trials). When the Japanese data were added to the data from the three European trials the CPMP concluded that: *"... the statistical evidence for the efficacy of riluzole is less secure. Nevertheless ... the balance of probability is still in favour of riluzole."*

4.3.1.4 Adjusted analyses

All trials used the Cox proportional hazards model to perform adjusted analyses, although the Yanagisawa report does not give any detail of the model used or the results.

Unlike regression approaches with continuous outcome measures, the Cox model does not improve precision, and parameter estimates may be sensitive to violation of the proportional hazards assumption.[59] Although the Lacomblez paper does report an attempt to check this assumption, the available tests of proportional hazards are not powerful and a much larger sample size would be required to detect even quite substantial departures from proportionality.

It is not clear from any of the papers whether there was a prespecified list of covariates to be included in the adjusted analyses, or whether any covariates initially included were discarded from the model. Bensimon and Lacomblez both appear to have performed the adjusted analysis alongside construction of a prognostic index, but the authors do not give details of how these models were developed; only the Meininger report includes 'non-significant' covariates in the report of this analysis. For the Lacomblez data, however, the EMEA did request the results of the Cox model including all pre-specified covariates and noted that: *"As was anticipated, the P-values were less extreme (50mg p=0.082, 100mg p=0.003, 200mg p=0.001) but the levels of significance attached to the higher dose levels remained high."*

The covariates used in the adjusted analyses differed across the trials (see Appendix 8, page 63). The results of the adjusted analyses are thus not strictly comparable, as parameter estimates may be markedly affected by the inclusion or exclusion of other covariates. The results of these analyses have therefore not been formally combined. The adjusted results for each trial are summarised in Appendix 8 on page 63.
None of the adjusted analyses reported differ substantially from the unadjusted results, or results stratified by site of onset. The largest difference due to adjustment is reported by Lacomblez *et al*. This is perhaps surprising given that this is the largest trial with no apparent imbalances in patient characteristics at baseline, although even small differences in factors which are strongly prognostic could be responsible for such an effect. Uncertainties in model selection could also be responsible, although the EMEA did request a further adjusted analysis using direct stratification by risk factors in which "*similar levels of significance were achieved"*. Even so, if comparable adjusted analyses were available from all trials, it is unlikely that the pooled estimate from these analyses would be substantially (or practically) different from the unadjusted estimates reported above.

4.3.1.5 Timepoint for analysis and treatment effect over time

The results reported above are those for the entire period of follow-up reported for each trial, which was 18-21 months in each case. Bensimon *et al* state that their primary endpoint was survival at 12 months from randomisation, although they continued to follow-up patients after this time and report all data available up to 21 months from the start of the trial (at which point all placebo patients were offered riluzole); they note that the survival benefit appeared to be greater at 12 months than overall.

Lacomblez *et al* also reported results at 12 months as well as overall as they wished to examine the possibility, raised by the Bensimon data, that the treatment effect was greater in the first year from randomisation and also to examine the proportional hazards assumption underlying the use of the Cox model. They also report apparently greater benefit at 12 months, but the test for interaction by time was not significant. A much larger trial would be required to detect realistic differences in treatment effect over time, and so this analysis is far from conclusive.

Comparison of hazard ratios over different time periods may be useful, particularly for examining the assumption of proportional hazards (as done by Lacomblez *et al*). A particular period of follow-up is implicit in power calculations for survival analysis, as the 'effective sample size' is dependent on the number of events observed, and is thus a function of both the number of patients randomised *and* the period over which they are followed-up. However, methods for *analysing* survival data are designed specifically to deal with variable follow-up times, i.e. to account for censored data. Unless there is a very clear *a priori* rationale, it is inappropriate (and wasteful) to emphasise survival results at a particular timepoint rather than using all data available from the entire period of follow-up. The hazard ratio for the full data set, along with the Kaplan-Meier survival curves, provides the most appropriate and reliable summary of treatment effects in the patient population recruited to the trial.

For these trials it is perhaps worth examining the implications of this approach compared to an analysis based on data at 12 months. Both Bensimon and Lacomblez report somewhat more favourable results at 12 months, although neither report gives undue emphasis to this result compared to the longer term data. The combined data from these trials is insufficient to allow any clear statement about changes in treatment effect over time. If we assume that there is in fact no difference in long-term compared to short-term effects, then the longer-term result gives a more reliable estimate of the true treatment effect, and is thus preferred. If, on the other hand, we assume that any benefit does in fact decrease with time, then results based on short-term data are misleading, as they do not reflect the experience of patients who live (are 'event-free') beyond this timepoint. It is worth noting that if short-term benefit is high compared to the benefit overall (survival curves are 'banana-shaped' and converge rapidly) then the *total* gain may be *less* than that obtainable if the overall benefit were smaller but constant over time (survival curves are more like a ski-slope and remain separated for longer).

We have therefore not summarised 12 month data, as the overall results are more reliable, more informative and thus more appropriate.

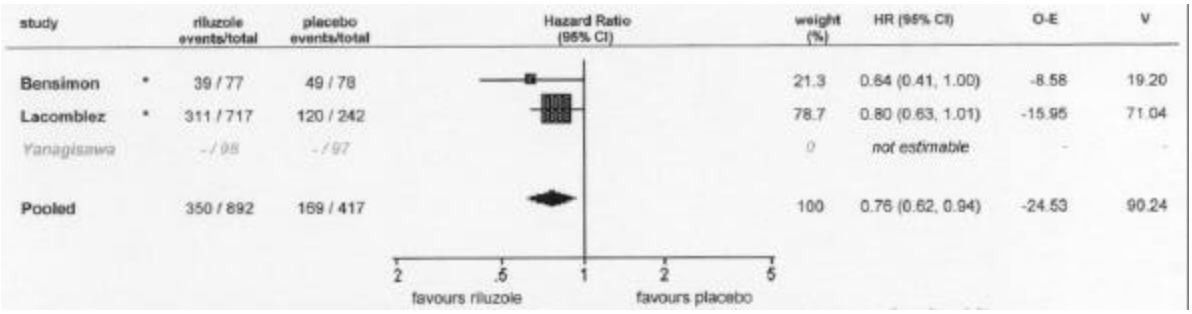
Although we would have liked to examine the possible dependence of treatment effect on time, it has not been possible to do this due to the small numbers of patients randomised and the lack of long-term follow-up. Unfortunately, placebo patients in these trials were offered riluzole at the end of follow-up (16-21 months), and so even if it were available additional, long-term comparative data from these trials would be difficult to interpret.

4.3.1.6 Heterogeneity

There is no significant statistical heterogeneity in these results; the addition of the results from the Yanagisawa trial is unlikely to substantially increase heterogeneity. However, the test for (statistical) heterogeneity is not particularly powerful, and the results from both the Meininger and Yanagisawa trials, although small, are somewhat discordant with the Bensimon and Lacomblez data.

There is some clinical heterogeneity between the trials. In particular Meininger recruited a very different patient population from the other trials. This trial was run in parallel with the Lacomblez trial and was designed specifically for patients who would be ineligible for the Lacomblez trial due to age, > 5 years disease duration or low FVC. Entry criteria for the Meininger trial were essentially defined as ineligibility for Lacomblez and the trial thus included patients who were older than 75 *or* with >5 years duration of disease *or* with FVC<40%. In order to investigate the impact of this trial on the pooled results, we repeated the analysis excluding this trial. The results are presented in Figure 2 below.

Figure 2 - Results excluding Meininger trial



*data not directly reported; results estimated using summary data from Kaplan-Meier survival curves (see Appendices 7 and 8)

Although the Meininger trial was 'negative', it is a small trial and the exclusion has no substantial impact on the pooled results; the pooled hazard ratio from Bensimon and Lacomblez combined is 0.76 with a 95% confidence interval of 0.62 to 0.94. As before, the results stratified by site of onset are similar, with a pooled hazard ratio of 0.78 and a 95% confidence interval of 0.65 to 0.94. It is unlikely that inclusion of the results from the Yanagisawa trial, although also 'negative', would have a substantial practical impact on these results.

There is thus *some* evidence that riluzole confers a small survival benefit in the patient group recruited to the Bensimon and Lacomblez trials. These patients were similar to those recruited to the Yanagisawa trial; there are no substantial differences apparent in the reported patient characteristics between these three trials.

There is no evidence of a benefit for the group with generally more advanced disease excluded from these trials but included in the Meininger trial. However, the lack of evidence is due to the small size of this trial, the only one which included this patient population, and the results cannot be interpreted as evidence of no benefit in this (somewhat heterogeneous) group. Eligibility for the Meininger trial was essentially defined as *in*eligibility for Lacomblez, and the trial thus included patients who were older than 75 or with >5 years duration of disease or with FVC <40%.

4.3.1.7 Treatment effect in subgroups; effect by site of onset

All four trials investigated subgroups by site of onset (bulbar and limb).

Bensimon *et al* report a (quantitative) difference in treatment effect between the two groups, although it is not clear what methods (if any) were used to investigate the interaction. The authors note that their results show a substantial benefit in favour of riluzole for patients with bulbar onset but little apparent benefit for those with limb onset.

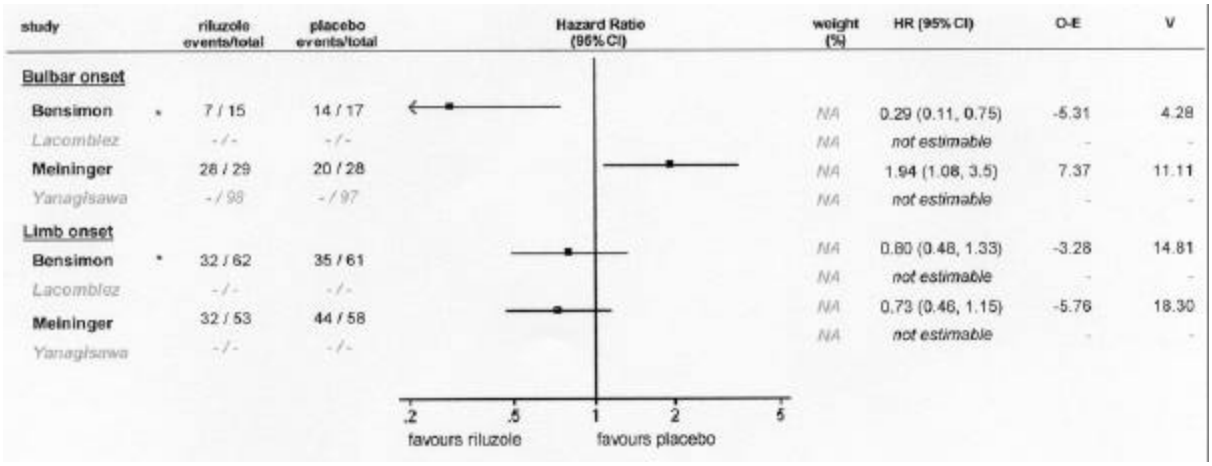
Following the report of Bensimon *et al*, the confirmatory trial by Lacomblez *et al* also investigated the possibility of an interaction between treatment and site of onset, using a much larger data set. They report that there was no significant interaction (p=0.62, investigated using the Cox proportional hazards model). For this reason, they do not report results separately for the two groups.

Meininger *et al* report a significant (qualitative) interaction between treatment and site of onset (reported p-value for interaction <0.01, investigated using the Cox proportional hazards model). Examination of the treatment effect within groups indicated a moderate benefit associated with Riluzole in patients with limb onset and a substantial detriment in those with bulbar onset. Note that the direction of the interaction reported here is the opposite to that reported by Bensimon *et al*, who found Riluzole to be of greatest benefit for patients with bulbar onset.

The results for progression-free survival reported by Yanagisawa *et al* do not indicate any interaction, although this trial, like Bensimon and Meininger, is small.

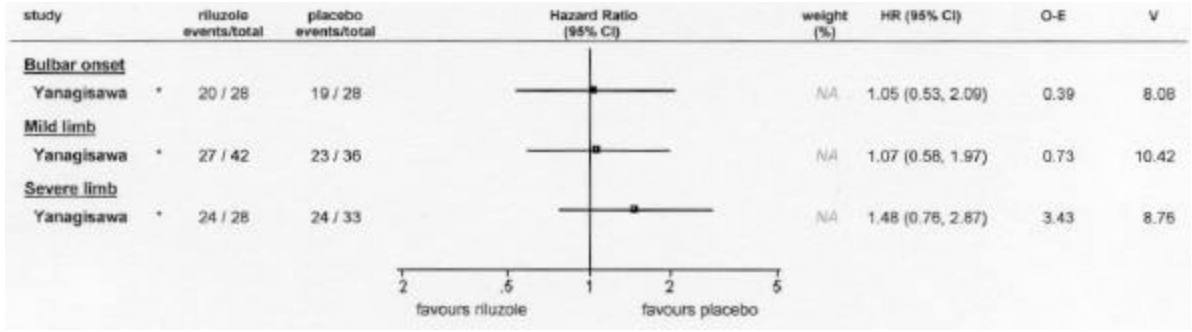
No formal subgroup analysis of the pooled data is undertaken here, as no within group estimates are available from the largest trial (Lacomblez, ~60% of the data set). Where comparisons were reported separately for the two groups, these data are summarised in Figure 3 below. Results for tracheostomy-free survival in the Yanagisawa trial are not reported for all groups and so are not included in the figure; progression-free survival data from this trial are summarised separately in Figure 4 below.

Figure 3 - Treatment effect by site of onset - Tracheostomy-free survival



*data not directly reported; results estimated using summary data from Kaplan-Meier survival curves (see Appendices 7 and 8)

Figure 4 - Treatment effect by site of onset - Progression-free survival (Yanagisawa *et al*)



*data not directly reported; results estimated using summary data from Kaplan-Meier survival curves (see Appendices 7 and 8)

There are clearly some differences between these trials in the results of subgroup analyses by site of onset. Two trials, including the largest, report no evidence of an interaction, whilst the other two trials (Bensimon and Meininger) both report a possible interaction but disagree as to the direction of the interaction. Subgroup analysis, particularly with trials as small as these, is notoriously unreliable. It is difficult to draw firm conclusions from the data available but, on the basis of what has been reported, there is no clear evidence of any interaction between treatment and site of onset.

4.3.1.8 Treatment effect in subgroups; effect by "high" and "low" risk

Lacomblez *et al* derived a prognostic index using the Cox model and used this to divide patients into two equal groups according to risk (above and below the median 'risk' score). The later Yanagisawa paper repeated this analysis; they updated the prognostic index derived by Lacomblez by combining their data with that of Lacomblez and Bensimon (although some patients appear to have been excluded) and then split their patients into two groups according to whether they scored above or below the median risk score for the whole data set combined. This led to only about one third (rather than half) of the Yanagisawa patients being defined as 'high risk', as might be expected from the difference in eligibility criteria, as the Japanese trial required an 'event-free' life expectancy of at least 6 months.

Yanagisawa *et al* do not give details of the updated prognostic index they derive using the combined data. If the two indices were broadly similar, this will have led to the cut-off (the median score of all patients combined) being at a slightly lower risk compared to that used by Lacomblez *et al*, but this difference will not be great due to the much larger numbers in the Lacomblez trial. The high and low risk groups reported by Lacomblez and Yanagisawa respectively appear to be quite similar in the two papers, with 40-50% of 'high risk' patients alive at 12 months and 80-90% of 'low risk' patients alive at 12 months.

Yanagisawa *et al* went on to investigate differences in treatment effect according to risk. Although the methods (if any) used are not clear, and the analysis did not involve the ITT population, they report finding a trend in favour of riluzole in 'high risk' patients only. This subgroup analysis, particularly in such a small trial, should be treated with caution. However, Yanagisawa *et al* state their motivation for the 'by risk' analysis:

"In overseas clinical studies performed for 18 months or shorter, riluzole was effective only in patients in whom primary endpoints occurred relatively frequently."

Although no such analysis is detailed in the other trial reports available to us, the European Medicines Evaluation Agency did request a similar analysis from Rhône-Poulenc Rorer based on combined individual patient data from the Bensimon, Lacomblez and Meininger studies. They report that:

"An analysis separating patients in two risk levels: "high risk" and "low risk" was a posteriori performed [at the request of the EMEA], based on an initial risk index calculated for each patient. Efficacy on survival was only apparent in "high risk" patients of studies 216 and 301 [Bensimon and Lacomblez], thus evidencing that a benefit on survival can only be demonstrated in patients having reached a certain degree of severity of the disease."

(Note that the final part of this statement is not strictly correct, unless it is assumed that 'risk' here is defined entirely by the stage of advancement reached, and is not related to the underlying rate of disease progression).

Unfortunately no further (numerical) information is available to us about the analysis performed for the EMEA or the statistical methods used. This possible interaction needs to be investigated further before any conclusions can be drawn. Careful analysis is required as apparent interactions may easily appear by chance. Furthermore, the effect may be an artefact of the period of follow-up, as pointed out by Yanagisawa and colleagues. All of these trials had very short follow-up (~18 months) and so few 'events' will have been observed in the 'low risk' populations; 'lack of an effect' could simply mean 'lack of power to detect an effect'. We cannot comment further without access to the data and/or more information about the methods used to examine the interaction.

4.3.2 Functional status

4.3.2.1 Definition of endpoints

All of the trials evaluated annual rates of deterioration in muscle strength, limb function and bulbar function. Lacomblez used a modified Norris scale for limb and bulbar function, with muscle strength assessed using the "scale of the Medical Research Council".[42] Bensimon, Meininger and Yanagisawa appear to have used the same instruments, although the scale for muscle testing is not described by these authors. Yanagisawa *et al* used the Japanese versions of the Norris scales for limb and bulbar function.

4.3.2.2 Data available

Bensimon, Lacomblez and Meininger report mean annual rate of deterioration, with estimates of the standard error. Results for these trials individually and combined are summarised in Table 6. Yanagisawa *et al* analysed percentage change from baseline, but do not report the results in any detail.

4.3.2.3 Results (functional status)

No numerical data on functional status is available from Yanagisawa *et al*, they say only:

"There were no significant differences between the treatment groups concerning secondary endpoints based on percentages of changes in function test scores from baseline".

The results for the other three trials are summarised in Table 6 below.

Table 6 - Summary of functional status; data are annual rates of deterioration

Data in **bold** text are reported directly in the trials reports; data in *italics* have been derived from information given in the trial reports. Combined results are summarised in the far right-hand column in ***bold italics***.

Muscle testing score (minimum score 0, maximum score 110)										
Trial	**Bensimon**			**Lacomblez***			**Meininger**			**Combined**
Group	**placebo**	**riluzole**	**difference**	**placebo**	**riluzole**	**difference**	**placebo**	**riluzole**	**difference**	**difference**
n	*n=75*	*n=75*		*not stated*	*not stated*		*n=68*	*n=64*		
Results	(points/yr)	(points/yr)	(points/yr)	(points/yr)	(points/yr)	(points/yr)	(points/yr)	(points/yr)	(points/yr)	(points/yr)
mean	**34.40**	**22.90**	**11.50**	*24.30*	*23.83*	*0.47*	**28.60**	**24.20**	*4.40*	***2.08***
se	-	-	**5.20**	*1.70*	*0.96*	*1.95*	**3.80**	**4.20**	*5.66*	***1.74***
95% CI	*NA*	*NA*	*1.31, 21.69*	*NA*	*NA*	*-3.35, 4.30*	*NA*	*NA*	*-6.70, 15.50*	***-1.33, 5.49***
p-value			**0.028**			*0.81*			**0.37**	***0.23***
Bulbar score (minimum score 0, maximum score 39)										
Trial	**Bensimon**			**Lacomblez***			**Meininger**			**Combined**
Group	**placebo**	**riluzole**	**difference**	**placebo**	**riluzole**	**difference**	**placebo**	**riluzole**	**difference**	**difference**
n	*n=75*	*n=75*		*not stated*	*not stated*		*n=68*	*n=64*		
Results	(points/yr)	(points/yr)	(points/yr)	(points/yr)	(points/yr)	(points/yr)	(points/yr)	(points/yr)	(points/yr)	(points/yr)
mean	**12.30**	**9.80**	**2.50**	*11.00*	*9.77*	*1.23*	**10.50**	**6.10**	*4.40*	***1.73***
se	-	-	**3.00**	*0.80*	*0.44*	*0.91*	**1.80**	**1.40**	*2.28*	***0.82***
95% CI	*NA*	*NA*	*-3.38, 8.38*	*NA*	*NA*	*-0.56, 3.02*	*NA*	*NA*	*-0.07, 8.87*	***0.13, 3.33***
p-value			**0.42**			*0.18*			**0.05**	***0.03***
Limb score (minimum score 0, maximum score 63)										
Trial	**Bensimon**			**Lacomblez***			**Meininger**			**Combined**
Group	**placebo**	**riluzole**	**difference**	**placebo**	**riluzole**	**difference**	**placebo**	**riluzole**	**difference**	**difference**
n	*n=75*	*n=75*		*not stated*	*not stated*		*n=68*	*n=64*		
Results	(points/yr)	(points/yr)	(points/yr)	(points/yr)	(points/yr)	(points/yr)	(points/yr)	(points/yr)	(points/yr)	(points/yr)
mean	**28.10**	**21.80**	**6.30**	*24.00*	*21.57*	*2.43*	**16.90**	**14.60**	*2.30*	***2.73***
se	-	-	**5.20**	*1.50*	*0.83*	*1.71*	**2.80**	**2.90**	*4.03*	***1.51***
95% CI	*NA*	*NA*	*-3.89, 16.49*	*NA*	*NA*	*-0.94, 5.79*	*NA*	*NA*	*-5.60, 10.20*	***-0.22, 5.69***
p-value			**0.22**			*0.16*			**0.40**	***0.07***

*all doses combined; means and standard errors estimated from plot (data not otherwise reported)

The combined data from these three trials do suggest a small reduction in the rate of deterioration in these functional outcomes. On the basis of the information available to us, it is impossible to say what effect the addition of the results from Yanagisawa *et al* might have on this analysis.

The estimated reduction in the annual rate of deterioration is around 2 points for each scale, although the annual rates of deterioration in each scale range from around 30 points (muscle testing) to around 10 points (bulbar score). The relative reduction in rate of deterioration is around 10-20% for each scale, although the confidence intervals are wide and thus consistent with much smaller or larger benefits.

It is not clear whether these differences are clinically significant. It is difficult to assess the meaning of a 2 point reduction in the annual rate of deterioration on any of these scales, and indeed whether this 2 point difference has the same meaning for a patient with a high initial score compared to one whose score is very low to begin with. There is no information given as to the relationship between rate of deterioration and initial score, or whether the absolute reduction was broadly similar for patients with high and low initial scores. More complex methods of analysis, such as analysis of covariance or longitudinal methods, would be more appropriate for this sort of data. It is not possible for us to consider these data in more detail without access to the individual patient data.

An important point to note here is that estimated differences in rates of change of functional status may be biased, given differences in survival between the two treatment groups. When there are observed differences in survival, longitudinal data collected from the survivors in each group are not strictly comparable. This is because there are a small number of patients who are 'alive and contributing data' on one arm whose counterparts in the other treatment group arm are 'dead and not contributing data'.

The effect of this 'informative censoring' may mask true effects, or give rise to spurious ones; assigning a 'zero' rate of deterioration to patients who have died would not be an adequate means of addressing the problem. Methods are available to adjust longitudinal measurements for survival differences, but these cannot be applied to the summary data available to us. These three trials present the data as annual rates of deterioration. No information is given as to intra-patient changes in rates of deterioration over time in each of these scales, which may be increasing, decreasing or constant. The likely effect of informative censoring in this case is therefore impossible to assess.

4.3.3 Adverse events and safety

In the three trials (Bensimon *et al*, Lacomblez *et al* & Yanagisawa *et al*) which reported the number of adverse events for individual treatment groups overall, these were roughly equal for placebo and riluzole. Trials by both Bensimon *et al* and Meininger *et al* reported around twice as many withdrawals for riluzole, as compared to placebo, whereas both Lacomblez *et al* and Yanagisawa *et al* report very similar number of withdrawals in each arm. The most frequently reported adverse events included respiratory disorders, dysphagia, asthenia, apnoea and nervous system disorders. Adverse events occurring more frequently in patients taking riluzole included increased ALAT or ASAT asthenia, nausea and abdominal pain. The adverse events involving ALAT and ASAT (liver function) confirm advice that riluzole should be avoided in patients with hepatic impairment.

A summary of adverse events is shown at Table 7.

Table 7 - Adverse events

	Bensimon *et al*[43] n=155		Lacomblez *et al*[44] n=959				Meininger *et al*[45] n=168		Yanagisawa *et al*[46] n=195	
	Placebo	Riluzole 100mg	Placebo	Riluzole 50mg	Riluzole 100mg	Riluzole 200mg	Placebo	Riluzole 100mg	Placebo	Riluzole 100mg
% with adverse event	91%	93%	90% reported adverse event. Numbers not given for individual treatment groups				91%	91%	18%	24%
% with treatment withdrawn	12%	25%	21%	21%	23%	22%	7%	14%	7% (Number of drop-outs for side-effects)	6%
Most frequent adverse events: Respiratory system							67%	54%	Conditions classed as mild/moderate/severe 1%	3%
Respiratory disorders	43%	39%								
Bronchitis			18%	17%	15%	14%				
Lung function decrease			13%	13%	14%	16%				
Asthenia	15%	26%	13%	15%	18%	20%			7%	5%
Dysphagia	11%	8%	20%	18%	20%	17%				
Nausea			13%	13%	21%	21%				
Apnoea			12%	10%	11%	8%				
Increased ALAT/ASAT	8%	17%								
Headache (inc. dull headache)									11%	8%
Muscle spasm/rigidity									5%	4%
Body as a whole							64%	52%		
Digestive system							19%	15%		
Cardiovascular system							8%	17%		
Nervous system							4%	7%		
Others									5%	8%
General									3%	6%

The European Agency for the Evaluation of Medicinal Products reported that of approximately 5,000 patients with ALS who took riluzole, three cases of neutropenia were reported. These all occurred within 2 months of riluzole treatment. No events on cognitive, cardiovascular or respiratory functions were observed.[58]

The Agency reported the number of adverse events that occurred in the trials by Bensimon *et al*, Lacomblez *et al* and Meininger *et al*, at a frequency of 1% or more in ALS patients on riluzole 100mg/day and were greater than placebo by 1% or were serious adverse events more frequent than placebo. These are shown at Table 8.

Table 8 - Adverse events occurring more frequently in riluzole than placebo

Adverse Events Occurring in **Placebo-Controlled Clinical Trials** Percentage of patients reporting events*		
	Riluzole 100mg/day (N=395)	Placebo (N=406)
Asthenia	17.5	11.3
Nausea	14.2	9.1
Headache	6.8	5.7
Abdominal pain	5.1	3.7
Pain	4.8	2.0
Vomiting	3.8	1.5
Dizziness	3.3	2.2
Tachycardia	3.0	1.5
Somnolence	2.0	1.0
Circumoral parasthesia	1.3	0.0
*Where riluzole incidence is greater than placebo by 1%		

5 RESULTS - HEALTH ECONOMICS

Summary of existing economic evaluations

- Eight economic studies were found
- Base-case ICER is highly variable, with up to a 5-fold variation, the most optimistic being the Tavakoli/Aventis model
- The key parameter driving the variation is the gain in life years
- The key assumption in estimating the gain in life expectancy concerns the extrapolation beyond observed survival
- All cost analyses were hampered by the fact that resource use data were not collected in clinical trials

Summary of the Birmingham economic model

- A model was developed to explore the uncertainties identified in previous analyses, from a health service perspective
- Survival data were taken from combined results of trials by Lacomblez *et al* and Bensimon *et al*, using an optimistic assumption in favour of the drug (all riluzole doses)
- Extrapolation beyond observed survival was undertaken using a Weibull model
- Base-case ICER gave a cost per life year £39,000 and a cost per QALY £58,000
- A sensitivity analysis indicates that the most optimistic ICER (cost per QALY) is £20,000 and the most pessimistic has riluzole dominated by placebo

5.1 Drug cost

The recommended dosage is 50mg bd (i.e. 100mg daily). Riluzole costs £286.00 per 56 50mg tablets, [30] which equates to around £3,700 per year. It should be noted that existing evidence does not indicate that this dose is any more beneficial than 25mg bd (see Appendix 9, on page 68).

5.2 Existing economic evaluations

5.2.1 Studies found

A total of eight economic studies were identified.[21,31,55,60-64] Four were original economic evaluations of riluzole published in peer-review journals,[61-64] two were systematic reviews that included some consideration of economic issues,[31,55] there was one review of an unpublished report[60] and one was the economic analysis reported in the Aventis submission to NICE.[21] A confidential unpublished report undertaken by the Benefit Research Group was obtained by the review team, but we were unable to get a response from the group in order to gain approval to quote from it. The focus for this section of the report is on the original analyses reported in peer-review journals and the new data reported in the Aventis NICE submission.

5.2.2 Study characteristics and results

Table 9 describes some of the key study characteristics and reports the results for the base-case cost-effectiveness analyses. All studies compared treatment with riluzole against service provision without riluzole, either 'standard therapy' or 'best supportive care'.

Gray (1998)[61] was the only study to consider the cost-effectiveness of different doses of riluzole. In the published literature, all studies have used a cost-effectiveness analysis framework, reporting the incremental costs per additional life-year for riluzole treatment. The only study that adopted a cost-utility approach is the Aventis NICE submission. (However, according to the published review of the report by the Benefit Research Group, that also contained a cost-utility study.[13])

As is shown in Table 9, the base-case results relating to survival and costs reveal marked disparities between studies. Only three studies (Gray, Ginsberg & Lev and Messori *et al*) report these parameters - the study by Tavakoli *et al* and the Aventis submission only provided the base-case incremental cost-effectiveness ratio (ICER) and do not report base-case parameters for costs and survival separately. Unsurprisingly, the base-case ICERs also varied widely between the studies.

In an attempt to understand why the studies have come to such different conclusions regarding the cost-effectiveness of riluzole, the data and assumptions used in constructing the base-case analyses were explored (Table 10) and the sensitivity analyses undertaken were reviewed (Table 11). The results of this analysis are reported in the following four sections.

Table 9 - Assessment of published cost-effectiveness analyses of riluzole: study characteristics and results

	Study				
Criterion	Gray, 1998[61]	Ginsberg and Lev, 1999[62]	Messori *et al*., 1999[63]	Tavakoli *et al*., 1999[64]	Aventis NICE submission
Comparators	Riluzole treatment (100mg or 50mg) vs placebo	Riluzole treatment (100mg) vs care without riluzole	Standard supportive therapy plus riluzole (100mg) vs standard supportive therapy without riluzole	Riluzole treatment (100mg) vs best supportive care (as proxied by placebo group in trial)	Riluzole treatment (100mg) vs best supportive care (as proxied by placebo group in trial)
Perspective	Health sector	Health sector and society	Health sector	Health sector	Health sector
Type of economic evaluation Base-case survival result	CEA (incremental cost per life-year gained) Life-years gained: 50mg: 0.041; 100mg: 0.089	CEA (incremental cost per life-year gained) and CBA Assumptions: 3 year life expectancy for patients with ALS which is extended by 3 months using riluzole	CEA (incremental cost per life-year gained) Mean lifetime survival (discounted months): riluzole 19.7; standard therapy 17.4	CEA (incremental cost per life-year gained) Not stated (but estimated survival curves displayed)	CUA (incremental cost per QALY gained) Not stated
Base-case cost result: incremental costs of riluzole	Riluzole 50mg: £1860 Riluzole 100mg: £3984	Health sector costs only: $US 757 Health sector costs plus productivity savings: $US –2884	$US 11,966	**Not stated**	Not stated
Base-case ICER	Riluzole 50mg: £45 630 per life year-gained Riluzole 100mg: £44 890 per life year-gained	Health sector perspective: $US12,013 per life year gained Societal perspective: dominance (i.e. negative costs, positive benefits)	$US 62,609 per life-year gained	£8,587 per life-year gained	£12,384 per QALY gained
Funding / sponsorship	None acknowledged	Israeli Ministry of Health	None acknowledged	**Rhone-Poulenc Rorer**	Aventis

Table 10 - Assessment of published cost-effectiveness analyses of riluzole: effectiveness and cost data

Criterion	Study				
	Gray, 1998[61]	Ginsberg and Lev, 1999[62]	Messori *et al*., 1999[63]	Tavakoli *et al*., 1999[64]	**Aventis NICE submission**
Source(s) for survival data	Bensimon *et al* and Lacomblez *et al*. (for riluzole group, patients treated with either 50mg or 100mg)	Not stated / Assumption	Bensimon *et al* and Lacomblez *et al*. (for riluzole group, only patients treated with 100mg)	Lacomblez *et al*. (for riluzole group, data from all patients used regardless of dose)	Lacomblez *et al.* (for riluzole group, data from all patients used regardless of dose)
Analysis of survival data	Survival months lost and life-years gained No extrapolation beyond trial end	Not stated	Pooled survival analysis (log-rank and Cox) Extrapolation to lifetime survival through Gompertz analysis	Markov model based on (a) observed trial data and (b) extension of the 18-month transition probabilities for both groups 'using linear interpolation between successive probabilities'	Markov model based on (a) observed trial data and (b) extension of the 18-month transition probabilities for both groups 'using linear interpolation between successive probabilities'
Quality of life data	Not considered	Not considered	Not considered	Not considered	Standard gamble & EQ-5D VAS
Resource use data	Drug costs and tracheostomy costs only	Costs (savings) associated with hospitalisations, serum ALT testing, OP costs, drug costs and other medical costs	Drug costs and patient monitoring only	Costs of care for patients with ALS health states, drug costs and patient monitoring	Costs of care for patients with ALS health states, drug costs and patient monitoring
Source(s) for cost data	Published or routine sources	Published or routine sources	Published sources	Costs of care for patients with ALS health states from Munsat *et al.* Other costs from routine sources	Costs of care for patients with ALS health states from Munsat *et al.* Other costs from routine sources
Analysis of cost data	Simple calculation	Simple calculation	Simple calculation	Simple calculation	Simple calculation
Price year	1997	1996	1996	1996	1999
Discounting	No discounting	Costs and benefits discounted at 5%	Both life-years and costs discounted at 3%	Life-years not discounted Costs discounted at 6%	Life-years not discounted Costs discounted at 6%

Table 11 - Assessment of published cost-effectiveness analyses of riluzole:sensitivity analyses

	Study				
Criterion	Gray, 1998[61]	Ginsberg and Lev, 1999[62]	Messori *et al*., 1999[63]	Tavakoli *et al.*, 1999[64]	Aventis NICE submission
Approach	1-way	1-way	1-way	1-way	1-way & 2-way
Parameters	Quality of life adjustment (simple assumptions) Cost of tracheostomy (simple assumption)	Survival with ALS without riluzole (18 months to 24 months) Riluzole-induced extension to life expectancy (1 month to 5 months)	Survival gain (lower and upper 95% confidence limits) Drug price (substituted US price for UK or Italian price) Other health service cost per patient (estimate used by Ginsberg & Lev)	Costs of each health state experienced by patients with ALS	Benefits discounted Standard gamble/VAS utility scores Health states
Results	Results sensitive to quality of life assumptions	Results highly sensitive to variation in survival gain	ICER highly sensitive to variation in survival gain	Results not highly sensitive to variation in the cost of care	Results not highly sensitive to variation in any of these parameters

5.2.2.1 Analysis of survival data

Survival data for two of the economic analyses (Gray and Messori *et al*) were drawn from two of the published trials (Bensimon *et al* and Lacomblez *et al*). Given that the analysis by Gray (1998) considered the cost-effectiveness of alternative doses, survival data for each dose were analysed separately. Messori *et al* used data for patients in the 100mg riluzole trial arm only. The analysis reported by Tavakoli *et al* and the Aventis NICE submission used data from only a single trial (Lacomblez *et al*) and included data for all riluzole arms; the cost-effectiveness of doses other than 100mg was not explored. Ginsberg & Lev did not state the source of their survival estimates.

The five evaluations are very different in the way that the survival data have been analysed for the economic evaluations. The key parameters that require estimation are mean life expectancy with riluzole and mean life expectancy without riluzole. Whilst such data provide an indication of the incremental gain in survival, they are also necessary for the cost analysis since the assumption is generally made that riluzole will be taken until the patient's death. In all trials patients on placebo were switched to riluzole at the end of follow-up and so no longer-term survival data for placebo patients is available. The implication of this is that extrapolation beyond the follow-up data observed in the trials is required (i.e. extrapolating from *observed survival* to *predicted life expectancy*). Gray did not extrapolate beyond the trial end, and Ginsberg & Lev made no reference to the issue of survival extrapolation.

Messori *et al* applied a Gompertz model to the survival curves (reproduced in figure 5) that allowed survival curves to be extrapolated and mean lifetime survival to be estimated (as area under the survival curve). The base-case analysis reported a difference in mean lifetime survival between trial arms of 2.4 months (undiscounted). The Gompertz model represents one possible approach to extrapolation and the authors did not justify their choice of this approach. It would have been useful if, as part of their sensitivity analysis, the authors had explored the robustness of the results to alternative models, such as Weibull or exponential (Note: this is done in our analysis reported later in this section of the report.).

Tavakoli *et al* (and the Aventis NICE submission) adopted an alternative approach: the Markov model. Using data from the Lacomblez *et al* trial and the re-analysis of the data reported by Riviere *et al*, a Markov model was constructed to estimate survival from the point of entry into the trial through to death for all trial patients. The authors indicate that transition probabilities were used that were allowed to "vary by time" although no indication is given on how this was achieved. The paper reports observed survival (in the trial) and predicted survival (using the Markov model) through the presentation of survival curves shown as Figure 6 (reproduced from Tavakoli *et al*). The authors suggest that "for the first 18 months of the trial data both arms of the Markov model follow the Kaplan-Meier curve accurately".

Figure 5 - Messori *et al* - Gompertz extrapolation of survival

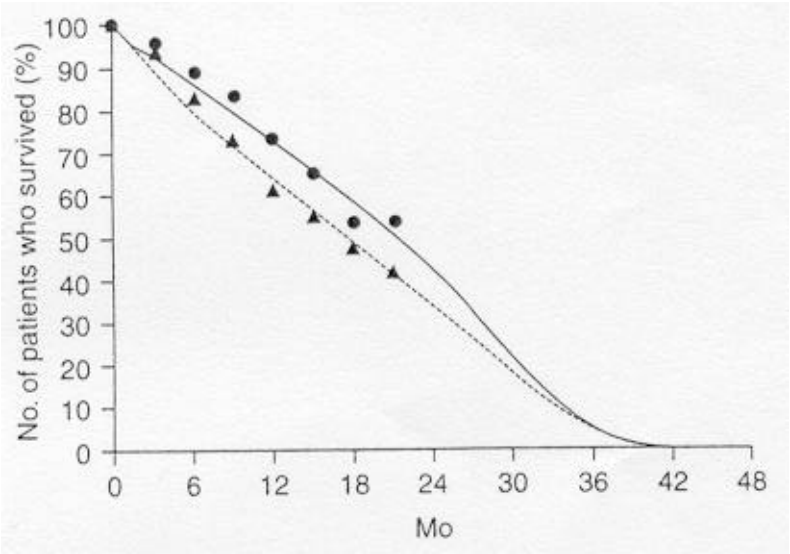
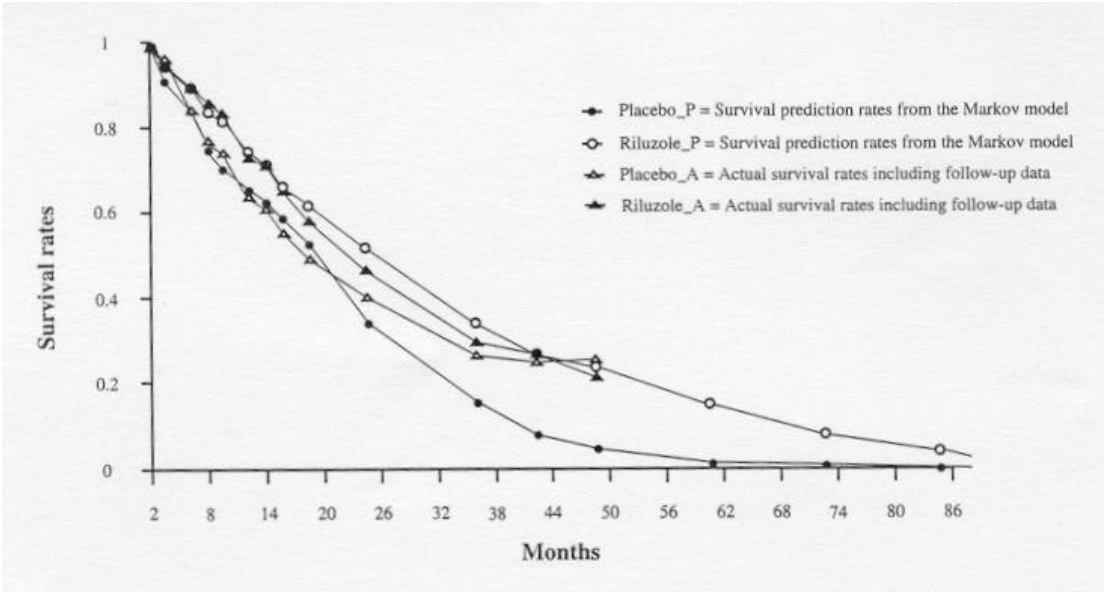


Figure 6 - Tavakoli *et al* - observed and predicted survival



It is not clear from Figure 6 that this statement is strictly correct. The divergence between the predicted survival curves for riluzole and placebo is, however, most prominent after 18 months, for which no unconfounded comparative observed data exist. Between 18 months and 36 months the predicted survival curve for riluzole is consistently above the observed survival for the riluzole cohort from the trial. The authors explain the process of estimation beyond 18 months as follows:

> *"in order to assess the long-term effects of riluzole on survival, the 18-month transition probabilities for both cohorts (riluzole and best supportive care) were extended using linear interpolation between successive probabilities and the process was ended when over 99% of patients from the cohort entered the dead state."*

It is not clear what this statement means. The estimated difference in mean lifetime survival between the riluzole and placebo groups appears to be about 12 months in this analysis (Note: this survival gain is not reported in the paper – the estimate is derived from visual inspection of two figures in the paper by Tavakoli *et al*). The general conclusion on the survival analysis reported in this paper (and the Aventis NICE submission) is one of caution: there is not enough information to allow a judgement on whether or not the Markov model has been used appropriately, and the estimate of lifetime survival gain is very different from that reported by Messori *et al* (and that reported later in this report).

5.2.2.2 Cost-utility analysis

The only available cost-utility analysis is that reported in the Aventis NICE submission. Utility scores for four ALS health states were collected from a small sample of patients with ALS in each of the four states (n=15, 21, 21 and 19 for states I to IV respectively). The health states used are those defined by Riviere *et al*, shown in Table 12, page 40. Elicitation of utility scores was undertaken using direct standard gamble questions and indirectly using EQ-5D. The reported scores for EQ-5D were those obtained using the VAS component of the instrument – these do not represent health state utilities since the VAS is anchored by 'Best imaginable health state' and 'Worst imaginable health state' and not 'Full health' and 'Death' as required for adjustment of life years in constructing estimates of quality-adjusted life years (QALYs). It is surprising that utilities for EQ-5D data were not reported using the University of York MVH Tariff.[65] It is not stated in the report whether the standard gamble or EQ-5D VAS scores were used in the cost-utility analysis.

Table 12 - ALS health states

State I (Mild)
Recently diagnosed
Mild deficit only in one of the three regions (speech, arm, leg)
Functionally independent in speech, upper extremity, activities of daily living and ambulation

State II (Moderate)
Mild deficity in all three regions
Moderate to severe deficit in one region while the other two regions are normal or mildly affected

State III (Severe)
Needs assistance in two or three regions
Speech is dysarthric and/or patient needs assistance to walk and/or needs assistance with upper extremity functions and activities of daily living

State IV (Terminal)
Non-functional use of at least two regions and/or moderate or non-functional use of the third region

5.2.2.3 Cost data

For the cost analyses, all evaluations were hampered by the fact that resource use data were not collected within the clinical trials. Therefore, all cost analyses are relatively simple although that conducted by Tavakoli *et al* draws upon published UK unit costs for ALS health states, reported by Munsat *et al.*[66] However, the estimates of time in each health state were derived from the Markov model and so they should be viewed with some caution given the earlier discussion. Only one study (Ginsberg and Lev) considered a broader perspective: they included financial estimates of productivity losses and gains. In estimating lifetime drug costs Messori *et al* was the only study to appropriately make an adjustment to reflect the observed patient withdrawal from riluzole in the trials. In total 25% of riluzole patients withdrew from treatment in both the Lacomblez *et al* and Bensimon *et al* trials.

5.2.2.4 Sensitivity analysis

None of the studies conducted an extensive sensitivity analysis (Table 11). From the analyses conducted the unsurprising finding is that the cost-effectiveness results are highly sensitive to variation in the estimate of survival gain.

5.3 Economic evaluation

5.3.1 Base-case values and parameters

The parameters used in the base-case economic analysis undertaken for this review are reported in Table 13.

Table 13 - Base-case parameters for the economic analysis

Parameters	Value	Source
Undiscounted survival (months) with riluzole	21.38	Birmingham Review (Weibull extrapolation)
Undiscounted survival (months) with placebo	19.67	Birmingham Review (Weibull extrapolation)
Discounted survival (months) with riluzole	20.85	Birmingham Review (Weibull extrapolation)
Discounted survival (months) with placebo	19.24	Birmingham Review (Weibull extrapolation)
Proportion of patient withdrawals from riluzole	0.25	Bensimon *et al* and Lacomblez *et al* trials
Riluzole cost per daily dose (£)	10.21	£286 per 56 50mg tablets
Patient monitoring cost per month (£)	17	Tavakoli *et al*
Annual care cost – ALS health state I	1236.61	Munsat *et al*
Annual care cost – ALS health state II	834.28	Munsat *et al*
Annual care cost – ALS health state III	1771.42	Munsat *et al*
Annual care cost – ALS health state IV	3263.17	Munsat *et al*
Discount rate	6%	UK Treasury
Utility – ALS health state I	0.79	Aventis NICE submission
Utility – ALS health state II	0.67	Aventis NICE submission
Utility – ALS health state III	0.71	Aventis NICE submission
Utility – ALS health state IV	0.45	Aventis NICE submission

Price base: 1999

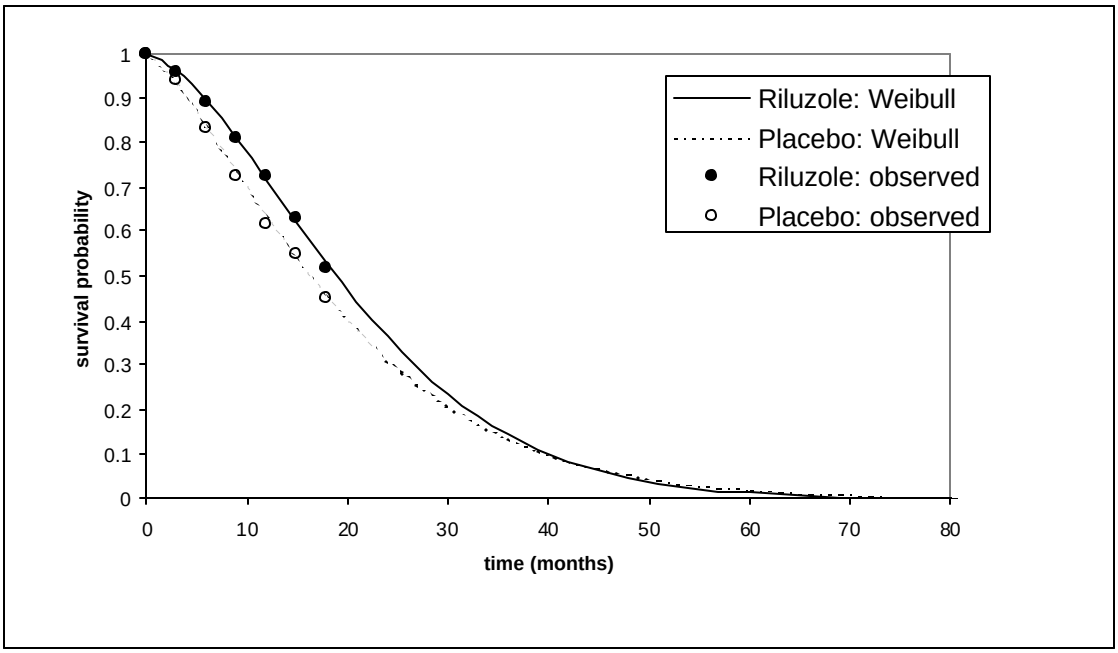
Where possible the economic analysis has used trial data or data from other published sources. The implication of using trial data in the base-case analysis is that the population of patients with ALS being considered is the same as that seen in the trials, which were dominated by prevalent (rather than incident) cases of ALS. The importance of this assumption is explored in the sensitivity analysis.

The survival estimates have been taken from the meta-analysis reported earlier in this report using data from the Bensimon *et al* and Lacomblez *et al* (all riluzole doses combined) trials only – the Meininger *et al* trial was excluded to avoided further heterogeneity in the patient group. Extrapolation beyond the observed survival in the trials has been undertaken using a Weibull model.[67] The survival curves resulting from this analysis are reported in Figure 7, below. The mean survival for patients in each group was estimated as the area under the survival curve. On the basis of the re-analysis of trial data reported by Riviere *et al*, on time spent in each ALS health state, an assumption has been in the base-case analysis that the increase in survival brought about by riluzole is experienced in ALS health state II.

The economic analysis adopted a health service perspective and so considered only costs incurred within the health sector. These included costs associated with the drug itself, the associated serum ALT testing, and the general costs of caring for patients with ALS over the extended survival period. For the base-case, all future costs and benefits were discounted at a rate of 6%. In the trials, it was observed that 25% of patients who began on riluzole withdrew from the treatment. The cost analysis has assumed that such a withdrawal rate would be seen in routine practice and cost estimates have been adjusted accordingly.

The economic evaluation includes both cost-effectiveness (cost per life-year gained) and cost-utility analyses (cost per QALY gained), both using an incremental approach with a focus on the increase in costs and increase in effectiveness. Data on quality of life were taken from the standard gamble utility estimates reported in the Aventis NICE submission.

Figure 7 - Survival curves with Weibull extrapolation



5.3.2 Base-case results

The results of the base-case economic analysis are reported in Table 14.

Table 14 - Base-case results for economic analysis

Results	Value
Lifetime cost of riluzole	£4841
Lifetime cost of monitoring	£242
Additional care costs due to survival increase	£112
Life-years gained	0.13
QALYs gained	0.09
Increase in costs	£5,200
ICER (cost per life-year)	£39,000
ICER (cost per quality-adjusted life-year)	£58,000

The results indicate that riluzole is associated with an increase in expected lifetime survival of 0.13 years which translates into 0.09 QALYs on the assumption that the gain is experienced in ALS health state II. The expected additional discounted cost to the health service is £5,200 per patient over the remainder of the patient's life.

5.3.3 Sensitivity analysis

The robustness of the base-case results was explored through the use of sensitivity analysis. Table 15, below provides an indication of the parameters that were varied. First, the importance of using the trial population with predominantly prevalent cases of ALS was explored. The assumption was made that all patients to receive riluzole would be incident cases and so the life expectancy of patients would be longer by about 2 years. This has implications for the total cost since riluzole is now being taken for a longer period and *may* have implications for benefits. However, there is currently no evidence upon which to base such an assertion. Therefore, two separate assumptions concerning survival gain were made independently: (1) the absolute increase in life-years for the incident population is the same as that seen in the trials; and (2) the absolute gain in life-years is greater for incident patients by the same proportion as the increase in the duration of therapy.

As indicated in the review of existing economic studies, the estimate of lifetime survival gain is a key driver of the results of the economic analysis. This suggests that the process of extrapolation beyond observed survival requires careful consideration. The Markov model used by Tavakoli *et al* (and the Aventis NICE submission) resulted in a predicted survival gain of approximately 12 months. This is very different to the predicted survival gain of 2-3 months by Ginsberg & Lev and Messori *et al*. In order to explore the importance of using a Weibull model for extrapolation in the base-case model, an alternative approach (a Gompertz model) was used in the sensitivity analysis to extrapolate survival for both placebo and riluzole groups, in line with Messori *et al*. This is shown in Figure 8. In addition, as a best-case scenario for survival gain with riluzole, the Gompertz model was used for placebo and the Weibull for riluzole; and as a worst-case survival scenario the Weibull model was used for placebo and the Gompertz model for riluzole. Estimates of survival gain in line with upper and lower 95% CI bounds were also explored.

The base-case analysis assumed that the survival gain was experienced in ALS health state II. This was varied in the sensitivity analysis to consider an equal share of the gain across all four ALS health states and, as a worst-case scenario for riluzole, of the gain being restricted to the terminal state (state IV). In addition, variation in the daily dose of riluzole and the discount rate were explored.

Figure 8 - Survival curves with Gompertz extrapolation

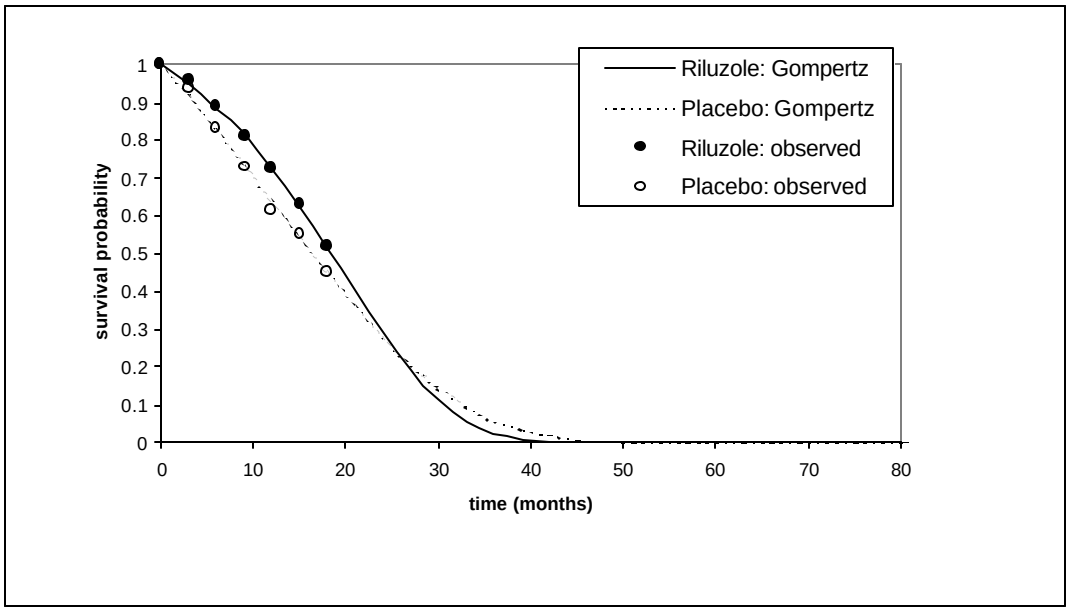


Table 15 - Sensitivity analysis results

Parameter	Gain in life-years	Gain in QALYs	Increase in cost (£)	ICER (cost per life-year)	ICER (cost per QALY)
Base-case result	0.13	0.09	5,200	39,000	58,000
Riluzole given to incident population (i.e. assuming that patients start taking riluzole 2 years earlier, on average, than trial patients)					
▪ assuming the same absolute gain in life-years as in the base-case	0.13	0.09	9,700	72,000	107,000
▪ assuming that the absolute gain in life-years is greater by the same proportion as the increase in duration of therapy	0.27	0.18	10,700	39,000	58,000
Variation in survival estimates					
▪ using a Gompertz model for survival extrapolation for both placebo and riluzole	0.08	0.05	4,500	59,000	88,000
▪ using a Gompertz model for placebo and Weibull model for riluzole extrapolation	0.31	0.21	5,300	17,000	25,000
▪ using a Weibull model for placebo and Gompertz model for riluzole extrapolation	-0.10	-0.07	4,300	-42,000*	-62,000*
▪ assuming 1 month survival gain for riluzole (as an estimate of the upper bound 95% CI)	0.08	0.05	5,000	66,000	98,000
▪ assuming 6 month survival gain for riluzole (as an estimate of the lower bound 95% CI)	0.47	0.32	6,400	14,000	20,000
Variation in health state assumption					
▪ survival gain distributed evenly across all 4 ALS health states	0.13	0.09	5,300	40,000	60,000
▪ all survival gain experienced in HS IV	0.13	0.06	5,500	41,000	91,000
Discount rate					
▪ benefits undiscounted, costs discounted at 6%	0.14	0.10	5,200	37,000	54,000
▪ costs and benefits discounted at 3%	0.14	0.09	5,200	38,000	56,000
Variation in dose of riluzole					
▪ 50mg per day	0.13	0.09	2,800	21,000	31,000

* Riluzole associated with higher cost and lower survival than placebo

Key points from the sensitivity analysis:

- The sensitivity analysis indicates that the base-case results are reasonably robust to variation in the health state assumptions and to discount rate variation.
- The cost-effectiveness of riluzole is, unsurprisingly, more attractive when a 50mg daily dose is used, assuming no reduction in effectiveness; there is no evidence to suggest that there is any difference in effectiveness between these two doses, although there is insufficient data to rule out the possibility of a moderate dose-outcome relationship.
- The use of riluzole in an incident population is associated with a marked increase in costs given the longer period of time over which the drug is taken. The impact of this on the ICER depends on the extent to which the gain in life-years is influenced by the earlier use of riluzole. There are no adequate published data that address this question.
- The sensitivity analysis reiterates the finding that a key driver of the cost-effectiveness result is the survival gain associated with riluzole. The use of alternative models to extrapolate beyond observed survival provide results that are vary widely. Further research is required to improve on the extrapolation process in this particular case. This might be achieved by using longer-term follow-up data for the riluzole cohorts of trial patients (all placebo patients were offered the switch to riluzole at the end of trial follow-up) and exploration of data on the natural history of ALS in the absence of riluzole.
- The plausible range is that the most optimistic ICER (cost per QALY) is £20,000 and the most pessimistic has riluzole dominated by placebo.

5.3.4 Limitations of the economic analysis

Survival extrapolation - would be useful to:

- Construct a simulation model to explore further the robustness of the longer term survival gain estimates.
- Have access to the further data on trial patients in the riluzole arms to observe survival beyond 18 months.
- Explore the natural history of ALS in order to facilitate improved estimation of survival without riluzole.

It would also be useful to obtain better data on:

- The effectiveness for lower dose (50mg) and for earlier use (i.e. for use in an incident population).
- The costs of caring for patients with ALS.
- The quality of life / utility data – based on a larger survey of patients than obtained in the Aventis submission. The individual variability of the values needs to be carefully considered.

5.3.5 Conclusions

The evidence presented in this report suggests that current estimates of the cost-effectiveness of riluzole must be viewed cautiously given the great uncertainties relating to many of the cost and benefit parameters. On the basis of the review and analyses presented in this section of the report, it is clear that the base-case economic analysis detailed in the Aventis NICE submission (and the paper by Tavakoli *et al* upon which the submission was based) is highly optimistic.

The principal benefit claimed for riluzole is an increase in survival. Some of the key remaining uncertainties on the benefits side for the economic analysis concern (1) the disease stage at which the survival gain is experienced, (2) the quality of life utility weights for ALS health states, and (3) the mean gain in life expectancy for patients who take riluzole. The central issue is the life expectancy gain. As indicated above, published estimates of the increase in survival range from 2 months to 12 months. It is clear that riluzole is associated with a net increase in costs to the health service. However, the magnitude of the increase is difficult to predict accurately. The main reason for this is uncertainty concerning the length of the period over which the drug will be administered.

A more robust estimate of the riluzole-induced gain in life expectancy is required to reduce current uncertainties concerning the appropriate methods of extrapolating beyond observed survival. Therefore, economic analysis in this area would be greatly improved through further research to strengthen the current estimates for the survival gain parameter. In particular, the current analysis would have been strengthened had the research team been given access to the longer-term survival data (up to 50 months) for riluzole held by Aventis.

6 PATIENT PERSPECTIVES

- Quality of life in ALS is not determined merely by functional state
- Some patients with ALS do not want to extend their lives
- Some patients do not think the side effects of riluzole are worth the benefits
- Some patients want the hope that riluzole represents, or need to feel they are fighting back
- The availability of riluzole does not alter the need for responsive palliative care

It is clear from the descriptions above that ALS is amongst the most serious of diseases. Moreover, it is a disease that most people know little about, people with ALS experience a steady loss of their ability to move and function, and an erosion of their autonomy.[2] They know that they have a relentlessly progressive and fatal disease. Problems are exacerbated by the involvement of the muscles used for speech (which eventually will affect some 80% of patients) as dysarthria can lead to impaired communication, isolation, frustration and low self esteem.[2] It is a disease that is also very distressing for family and carers.

The quality of life experienced by someone with ALS varies greatly from person to person even when they have the same objective functional impairment.[13] This is in part due to the individual's attitudes and values and in part to the degree of social support and care they receive.[68]

Riluzole is not a cure for ALS nor does it improve a patient's symptoms. The evidence suggests that it may extend time to tracheostomy or death by about three months and may slow the rate of deterioration of function, i.e. it may postpone the inevitable. Thus, even if riluzole is used, it is no substitute for good quality supportive and palliative care that is rapidly responsive to the changing needs of the patient.

"…care providers don't seem to understand how quickly this disease moves. If you need a stairlift, you need it now, not in six months."

A patient with MND quoted in the Times 25th July 2000.[68]

Riluzole is not without adverse effects and around 25% of patients withdrew from treatment in the trials. Since at best riluzole can only extend life and does not improve symptoms, the decision about whether treatment is worthwhile can only be made from the individual patient's perspective. A patient's physical condition and, more importantly, his or her subjective valuation of the quality of life that this imparts must be taken into account and this should be in a context of optimal symptom control and supportive care.

There is ample evidence that some people with ALS may not wish for their lives to be extended without improvement in their condition. Many have argued for access to physician-assisted suicide.[69] Ganzini *et al* (1998)[12] reported that over half of a sample of 100 patients with ALS said they would consider assisted suicide. Of these patients, most said that if physician-assisted suicide were legal, they would request a lethal prescription and keep it for future use. Although, only one person said they would use the prescription immediately. Care-givers generally shared the same attitude to assisted suicide.

The fact that some people either do not wish for their lives to be extended or do not think the adverse effects of riluzole are worth the gains is confirmed in a study by Rudnicki (1997)[70]. This study found that when riluzole was discussed with 46 patients with probable or definite ALS, only 17 chose to take the drug and 29 refused to take it. When giving explanations as to why they had refused it, 14 said it offered insufficient benefit, 9 cited high cost, 8 did not wish to prolong their lives, 2 felt the potential side effects were not worth the gain, 1 was in another study and 1 refused because it offered no gain in quality of life. Patients who had a shorter duration of either symptoms or confirmed ALS were more likely to take riluzole. Some patients had already participated in trials of alternative drugs such as IGF-1 or BDNF, and these were less likely to accept riluzole.

It was suggested that the way information is conveyed about riluzole to the patient could also have an effect on their decision as to whether or not to take it. The author reported that patients expressed concern that any prolongation of life would happen at the end of their life, when functional status was poor. The study concluded that *"…many ALS patients do not just wish to live longer, they want to live better".*

The Danish Institute for Health Services Research (1998)[13] undertook an in depth qualitative study of ALS patients and riluzole. They interviewed 12 patients, 10 of whom had chosen to take riluzole and 2 who had refused it. Eight relatives and 6 clinicians were also interviewed. It reports that ALS sufferers find themselves doubly in a powerless position - firstly because they have the disease, and secondly because treatment options are so limited.

This study confirmed that for some patients the harms of the treatment outweighed the potential benefit. The two people that had refused riluzole felt that the potential side effects were not worth the possibility of just 2-3 months of extra life.

> *"You hang onto life for as long as you can, but I don't want to feel awful whatever the price. Even if it might prolong my life by two or three months, I'll turn around and ask: What sort of two or three months they'll be, when I come to the end of it all"*
>
> Patient quoted in "Between Hope and Despair"[13]

Of those taking the drug, some patients did not experience side effects, others were affected by them to varying degrees. Four patients suffered side effects which were so severe that they discontinued their treatment. Others experimented with dosage to try and overcome side effects.

Both physicians and patients found it hard to distinguish the benefits and harms of the treatment from the natural disease process itself.

For some patients the need to have some hope or to be taking positive action against the disease were very important, even when they had a realistic understanding about the limited benefits riluzole could offer. This was particularly manifest in those that valued their current lives

"…I'm willing to try more or less anything…there was something to win and nothing to lose"

"I'd been told it could prolong your life. That was the reason why I said yes"

"If I'd said no, then once a few years had gone by, and I'd got worse, I would have risked having to sit there and say to myself "You were stupid" … it would be stupid to say no"

"…if it can delay it for the time being, so you don't collapse totally, then you might as well go ahead and take it…"

Even patients who do not wish to take the drug want the option to be available.[68] Some patients took riluzole in the hope of contributing to research and increase understanding, rather than for their own sake.[13]

"you can see how research leads to progress in a lot of other areas. And so it will here. But of course I'll be long dead before then. But that's really a secondary consideration - there'll be others after me. …That's why I agreed to take part. I just think you have to say yes."

The importance for some people of "doing something" was recently reiterated by Tricia Holmes, director of Care Development at the MND Association:

"This is a disease over which we have no control. It takes hold of people and removes their ability to live life as they choose. At the very least this drug [riluzole] gives people with MND the sense that they are doing something, and it offers hope, which is terribly important." [68]

In the Danish study[13] patients were generally well informed about riluzole and were satisfied with the level of information they had received from health professionals. However, faith in clinicians and their recommendation to try riluzole was an important factor for some patients.

From the health professionals' perspective, riluzole brought hope where there was previously none, but has limited effect, and has side effects that may reduce quality of life. One commented:

> *"…But if we ask what patients actually gain from this…then I have to admit that they get practically nothing. It's a matter of three months more, and we don't know what those three months will be like…"* [13]

There are no other specific treatments for ALS and some patients and health professionals strongly feel that on the grounds of equity this drug should be available for those who want it.

Clearly uptake rates are going to be influenced by the information about the drug and way it is imparted to patients. If patients with ALS are given accurate, accessible information about riluzole, many will choose not to take it, either because they do not wish to extend their lives without improvement in their symptoms, or because they do not think the limited extension of life is worth the harms and costs. Uptake rates could be as low as 30-40%, if the findings of Rudnicki's study[70] are generalisable. Although the fact that this study was carried out in the U.S. where the drug cost may have had a greater influence on the refusal of the medication than it would in the U.K.

For other patients any hope or opportunity to fight against this incurable disease is vitally important.

Both these facts mean that using average patient-derived quality of life scores for the health states associated with ALS, even if we assume that the extension of life occurs in the best of these states, will tend to underestimate the quality of life of those patients who would make an informed choice to use riluzole.

7 POTENTIAL METHODOLOGICAL STRENGTHS AND WEAKNESSES OF THE TECHNOLOGY ASSESSMENT

7.1 Strengths

- This review has systematically sought and incorporated data from all published and unpublished sources identified. It has used all existing data available. We contacted several subject experts in an effort to identify unpublished data. The review includes one trial not incorporated in previous published systematic reviews.
- Hazard ratios were used to combine the survival data, which is the only method which takes account of all of the available information.
- The economic analysis involved a rigorous assessment of the strengths and weaknesses of existing analyses, and built a further model to explore the impact of uncertainties revealed.

7.2 Weaknesses

7.2.1 Publication bias

- Although we contacted several subject experts to identify unpublished data, we cannot be sure that all unpublished studies have been found.
- There is some evidence of publication bias in the studies we have reported. The two 'positive' trials, were published in the New England Journal of Medicine and The Lancet (with 155 and 959 patients respectively). One 'negative' trial (n=168) remains unpublished, the other negative trial was published only in Japanese (n=195).

7.2.2 Missing data

- Further unpublished survival data have been produced for the study by Lacomblez *et al* (1996).[44]
- Results for tracheostomy-free survival were analysed by Yanagisawa *et al*, but these were not reported in sufficient detail for estimates to be included in this report.
- An analysis of individual patient data from all four of the trials identified in this review was carried out at the request of the EMEA, [58] but the full data have not been published.

Despite our contacting the authors and a request to the manufacturer via. NICE, these missing data have not been made available at the time this report was completed. However, a report of the individual patient data meta-analysis was received after this review was completed; a copy of this report accompanies this document, and we have given some brief comments in Appendix 10 on page 69.

7.2.3 Quality of existing data

- No survival data beyond 18-21 months are available to us.
- Since placebo patients were offered riluzole at the end of the follow-up periods in each of these trials, long term comparative data would be difficult to interpret, even if available.
- Although there were four trials, all were small, none having more than 244 patients in any randomised arm.
- There is limited information on the effectiveness of riluzole at the lower dose (50mg/day), and no evidence that this is any less effective than the current recommended dose of 100mg.
- There is little indication of the clinical importance of changes observed in the functional scales.
- There is very limited data on the impact on quality of life, and no comparative data.
- No cost data was collected in the RCTs.

8 DISCUSSION AND CONCLUSIONS

8.1 Implications of assessment findings

- There is limited evidence of a modest increase in tracheostomy-free survival for patients taking riluzole.
- However, the evidence base is restricted and uncertainty remains as to the true size of any treatment difference between riluzole and placebo.
- When costs and health economic impact extrapolating survival beyond that observed in trials are considered, the uncertainty about whether any benefits are worth the costs are magnified.
- Even under the most optimistic assumptions, riluzole at best postpones death for a few months, and does not preclude the need for supportive care and practical help.

8.1.1 Implications for the NHS

The evidence on effectiveness and health economic impact does not unequivocally indicate the best policy on the use of riluzole in ALS for the NHS. Policy makers may wish to take into account the fact that riluzole is the only specific treatment currently available for ALS. If riluzole is available it is important for patients to be given accurate information about its possible benefits and disbenefits, and that their final decision needs to be based on individual preferences.

If riluzole is available on the NHS, around 2,250 patients could receive it (since the estimated ALS population is 3,000, in 25% of whom it would be contraindicated). Many of these people, given accurate information about the likely benefits may choose not to take it. If all of them did, this would cost the NHS around £8.4 million per year. This represents £5.9 million above current expenditure on riluzole. The total additional annual cost to a district of 500,000 residents would be approximately £50,000.

Whether or not riluzole is used, good supportive care, including practical measures to assist activities of daily living that are timely and responsive to the rapidly changing needs of the patients remains essential.

8.1.2 Implications for patients and carers

Patients and carers should be given accurate information on the current evidence on the effectiveness of riluzole. They should be aware that riluzole does not cure ALS, and may not improve their quality of life. The evidence suggests that it may postpone death or tracheostomy by a few months, and there may be some small reduction in the rate of deterioration of functional status.

8.1.3 Implications for future research

8.1.3.1 Main uncertainties identified

- The size of any effect on survival, particularly in the longer term.
- The clinical significance of any changes in functional status.
- The impact on quality of life.
- Consequent uncertainty on health economic impact.

8.1.3.2 Research in progress

Miller *et al* (2000)[71] have reported some early results from the ALS patient care database in the USA. This was set up to provide neurologists with data to evaluate and improve their practices, examine temporal trends in the care of patients with ALS and develop hypotheses to be tested in formal clinical trials. The database is a large observational study, not a controlled trial.

The Health Services Research Unit at the University of Oxford is undertaking similar studies. Their ALS Health Profile and the ALS Quality of Life Scale studies aim to develop and validate a disease-specific health profile questionnaire and quality of life scale, respectively, for ALS.[72-74]

We understand that two trials of SR57746A, a novel agent in the treatment of motor neurone disease, are in progress by Sanofi Recherche. Results are expected at the end of 2000. Both trials evaluate SR57746A against placebo, and in one trial all subjects are also taking riluzole.[75]

A study in Holland is investigating the possible relationship between plasma and serum levels of riluzole and the level of cytochrome p450 1A2 activity, as well as the correlation between serum levels and side effects. A further study in Holland has recently begun recruiting 200 patients, which will investigate the effect of plasma and serum concentration of riluzole on disease progression and survival of patients with ALS.[76]

A range of studies which aim to explain ALS from an epidemiological perspective, or using surrogate markers are planned or underway.[21]

Other than those already identified, we are not aware of other clinical trials of riluzole in ALS, either underway, in progress or abandoned.[21] None of the identified research in progress directly addresses the uncertainties we have identified.

8.1.3.3 Suggestions for future research

Ideally, reliable information to address the uncertainties highlighted in this report would come from further trials. These RCTs should have survival follow-up through to death, an incident population and collection of health economic and quality of life data in parallel. The likely individual variability of the latter will need to be carefully considered. Additional questions which might be addressed in such trials include: whether there is a difference between short-term (e.g. one year) versus lifetime use of riluzole; whether 25mg bd is as effective as 50mg bd.

The feasibility of such trials might be doubted. However, in ALS there are around 120,000 newly diagnosed cases per year world-wide, and well over 1 million patients will have been diagnosed since the first trial started recruiting 10 years ago. Furthermore, patient perspectives suggest that lack of willingness to participate in such research may not be a barrier. Given these facts, it is disappointing that more and larger trials have not already been conducted.

Even if such trials were commenced now, it will be many years before further information will be made available. In the interim, uncertainty may be partly reduced by information from:

- New data on variation in uptake arising from varying clinician and patient views.
- Individual patient data meta-analysis of existing trial data to allow full examination of effects within subgroups and a more sensitive examination of effects on functional status.
- Existing ALS databases to allow more accurate extrapolation beyond observed survival in trials, both for patients who had been treated with riluzole and those who had not.
- Further data on past trial patients in riluzole arms to observe survival beyond 18 months.

9 APPENDICES

Appendix 1 - Advisory group of experts consulted

Advisory group of experts consulted, and why they were approached:

Dr Robert Miller	Main author of Cochrane Systematic Review on this topic, expertise in this area
Dr Keith Wheatley	Deputy Director of Birmingham Trials Unit, statistical expertise and specialist interest in riluzole
Dr Ammar Al-Chalabi	Researcher with specialist interest in ALS
Dr Gary Ginsberg	Health economist, specialist interest in riluzole

Possible competing interests

Dr Miller has accepted speakers honoraria from several pharmaceutical firms, including Rhône-Poulenc Rorer, the manufacturer of riluzole. He was an investigator in the trial by Lacomblez *et al* (1996),[44] but did not participate in data analysis or manuscript preparation. He was main author of a previous systematic review.[56]

Dr Wheatley has attended a meeting of the UK MND Advisory Panel, the expenses of which were paid by Excerpta Medica UK. The offered honorarium was declined, however. He is also preparing an independent review of riluzole.

Dr Al-Chalabi received a payment from Rhône-Poulenc Rorer towards travel/subsistence costs for an academic meeting in 1996, and has attended various meals sponsored by the company. He was awarded the 1999 Charcot Young Investigator for Research into ALS, which was co-sponsored by Rhône-Poulenc Rorer. The department where he works was one of the centres running the original trials into riluzole, and applies for scientific and educational grants from Rhône-Poulenc Rorer.

Dr Ginsberg presented a paper at two GP forums in England, the expenses of which were paid by Rhône-Poulenc Rorer.

Appendix 2 - List of clinical experts and specialist organisations contacted

Dr A Al-Chalabi	*MRC Clinician Scientist, Institute of Psychiatry, London*
Professor D Brooks	*Consultant Neurologist, Hammersmith Hospital, London*
Dr G Ginsberg	*Health Economist, Ministry of Health, Jerusalem, Israel*
Dr D Jefferson	*Consultant Neurologist, Queen's Medical Centre, Nottingham*
Professor N Leigh	*Consultant Neurologist, Institute of Psychiatry, London*
Dr R Miller	*Chairman, Department of Neurology, California Medical Center, San Francisco*
Professor D Mitchell	*Consultant Neurologist, Royal Preston Hospital*
Dr HS Pall	*Consultant Neurologist, Queen Elizabeth Hospital, Birmingham, UK*
Professor M Swash	*Consultant Neurologist, Department of Neurology, The Royal London Hospital*
Dr K Wheatley	*Deputy Director of Birmingham Trials Unit*

Motor Neurone Disease Association, Northampton, UK

Appendix 3 - Conference abstracts obtained

4th International Symposium on ALS/MND.
25-27 November 1993, Chantilly, Paris, France.

11th Tokyo Metropolitan Institute for Neuroscience (TMIN) International Symposium.
25-27 October 1995, Tokyo, Japan.

Association of British Neurologists Symposium.
18 September 1996, London, UK.

7th International Symposium on ALS/MND.
11 November 1996, Chicago, USA.

Meeting of the European Federation of Neurological Sciences.
6 June 1997, Prague, Czech Republic.

8th International Symposium on ALS/MND.
3-5 November 1997, Glasgow, Scotland.

48th European Neuromuscular Center Workshop on Drug Trials and Clinical Research in ALS.
12-14 January 1997, Narden, The Netherlands.

49th American Academy of Neurology Annual Meeting.
1997.

SEP/ALSA 1997.
20-22 January 1997, Missouri, USA.

Conference on Current Issues in ALS Therapeutic Trials.
2-4 April 1998, Virginia, USA.

9th International Symposium on ALS/MND.
16-18 November 1998, Munich, Germany.

10th International Symposium on ALS/MND.

15-17 November 1999, Vancouver, Canada (full abstract book obtained).

Appendix 4 - Functional scales for ALS

The original Norris scale combines ratings for a total of 34 parameters, consisting of 22 functional parameters, plus reflex activity, fasciculations, atrophy etc. Functional ratings are defined only as normal, impaired, trace or zero, and may be insensitive to change.[77] This has a maximum score of 100, and is shown at Table A4.1, below. The lower the score, the worse the functional state.

Table A4.1 - ALS scoring system, showing example scoring (taken from Norris *et al* 1974)[78]

Item	Weight	3 (normal)	2 (impaired)	1 (trace)	0
Hold up head		X			
Chew food		X			
Swallow		X			
Speak		X			
Turn in bed		X			
Sit up		X			
Empty bowel-bladder		X			
Breathe		X			
Cough		X			
Write name			X		
Use buttons, zippers			X		
Feed self			X		
Grip-lift self		X			
Lift book or tray		X			
Lift fork, pencil		X			
Change arm position		X			
Climb stairs, 1 flight				X	
Walk 1 block				X	
Walk across room			X		
Walk with assistance		X			
Stand up		X			
Change leg position		X			
			Hyper/hypo	Absent	Clonic
Stretch reflexes – arms			X		
– legs			X		
		Absent	Present	Hyper	Clonic
Jaw jerk		X			
		Flexor	Mute	Equivocal	Extensor
Plantar responses – right					X
– left					X
		None	Slight	Moderate	Severe
Fasciculation			X		
Wasting – face, tongue		X			
– arms, shoulders			X		
– legs, hips			X		
Labile emotions		X			
			0 to mild		Moderate to
Fatigability		—	X	—	severe
Leg rigidity		—	X	—	
Totals in example	81	= 57	+ 22	+ 2	+ 0
Theoretical totals	100	= 96	+ 4	+ 0	+ 0

The trial by Lacomblez *et al* used a modified Norris scale, which is subdivided into categories for manual muscle testing, bulbar function and limb function. This is shown at Table A4.2, below.

Table A4.2 - Functional Scales for ALS (taken from Lacomblez *et al*[42])

Manual muscle testing	Modified Norris bulbar scale	Modified Norris limb scale
I. Upper limb strength*	Blow	Hold up head
Thumb opposition	Whistle	Turn in bed
Wrist flexion	Blowing out cheeks	Sit up in bed
Wrist extension	Jaw movement	Writing ability
Elbow flexion	Clicking tongue	Buttoning, zipping
Elbow extension	Tongue protrusion	Dress oneself with a shirt, a
Shoulder abduction	Tongue against the cheek	blouse
	Tongue against the palate	Dress oneself with pants, a
II. Lower limb strength*	Cough	skirt
Ankle dorsiflexion	Hypersialorrhea	Cutting meat
Knee flexion	Nasalization	Holding a fork
Knee extension	Speech: mumbling	Filling up a glass and
Hip flexion	Swallowing: food	drinking from it
		Standing up and shaking
III.Neck	Gradation of items 1 to 9:	hands
Neck flexion	none	Combing one's hair
Neck extension	moderate	Brushing one's teeth
	impaired	Lift book or tray
Gradation of items:	normal	Lift fork or pencil
no contraction		Change arm position
flicker of trace contraction	Gradation of items 10 to 12:	Climb stairs
active movement with	severe	Walk around a block
gravity eliminated	present	Walk alone
active movement against	moderate	Walk with assistance
gravity but not against	absent	Stand up
resistance		
active movement against	Gradation of item 13:	Gradation of terms:
gravity and resistance	½ liquid	none
normal power	minced	moderate
	tender	impaired
	normal	normal
	(If food is given though	
	gastric tube, swallowing	
	must be rated 0)	

Each item of upper and lower limb is scored for the right and left side separately

Appendix 5 - Summary of systematic reviews identified

Three previous systematic reviews have been published,[31,55,56] as well as a marketing authorisation report which evaluated all of the four trials included in this review.[58]

Booth-Clibborn *et al* (1997)[31] included trials by Bensimon *et al*, Lacomblez *et al* and Meininger *et al*. The marginal costs of riluzole therapy were described and a number needed to treat (NNT) of six was calculated for early stage patients (i.e. six patients would be need to be treated with riluzole to delay one death or tracheostomy at 18 months). They estimate the lifetime cost of riluzole treatment to between £11,000 and £19,000, assuming 3-5 years survival. As it costs £33,500 to treat six patients with riluzole for 18 months, this would be the cost of preventing one death or tracheostomy at 18 months. Although they noted that a delay in death or tracheostomy had been observed at 18 months, uncertainties about the duration of the delay and quality of life during this period led to the conclusion that there was insufficient evidence to support riluzole treatment.

Chilcott et al (1997)[52] included trials by Bensimon *et al* and Lacomblez *et al.* Their cost-effectiveness analysis was based on the trial by Lacomblez *et al*, and focused on the 100mg treatment group. Two cost-benefit analyses were carried out, one adjusted for differences between prognostic characteristics and the other unadjusted. The cost per life year gained over 18 months was estimated to be around £50,000, or as low as £22,000. When adjusted for prognostic factors and modelled over 10 years, the mid-range estimate was £27,600. They felt unable to support the funding of riluzole, due to the uncertainties in the interpretation and analysis of survival, lack of quality of life information, limited claimed benefit and high cost-effectiveness ratio.

Miller et al (2000) [56] included trials by Bensimon *et al* and Lacomblez *et al*. Primary and secondary endpoints of the two trials were assessed, and a meta-analysis performed. They concluded that the benefits of riluzole at 100mg/day were modest but definite.

The Committee for Proprietary Medicinal Products (CPMP) of the European Agency for the Evaluation of Medicinal Products produced a European Public Assessment Report (1996, revised 1999),[58] describing a marketing authorisation for riluzole in the European Union. The report incorporated all of the four trials included in this review. The CPMP reported that riluzole had demonstrated a modest extension of life or the time taken for the progression of the disease to mechanical ventilation, in ALS patients other than those who are in the late stages of the disease. Adverse events and side effects were also reported. The CPMP concluded that riluzole showed adequate evidence of efficacy and a satisfactory risk/benefit profile, and recommended its marketing authorisation. Following authorisation, the CPMP requested the manufacturer to carry out a meta-analysis of individual patient data, including the trial by Yanagisawa *et al*, which had not previously been submitted. Following the evaluation of the meta-analysis, the statistical evidence for the efficacy of riluzole was less secure, but it was felt that the balance of probability was nevertheless in favour of riluzole.

Appendix 6 - Summary of clinical effectiveness studies excluded

Riviere *et al* (1998)[47] re-analysed data from the study by Lacomblez *et al* (1996),[44] using a classification of discrete health states. A significant difference was shown between riluzole and placebo groups in only one (mild) health state. The analysis was post-hoc and is seen as a preliminary study, requiring further confirmation.

Sojka *et al* (1997)[48] compared symptom progression both before and during administration of 100mg/day of riluzole, in a case series of five patients with ALS. The effect of riluzole in the patient group was highly variable, ranging from no effect to accelerated progression of symptoms. The authors suggest that ALS patients may not constitute a homogenous group with respect to the efficacy of riluzole treatment. The fact that this is a very small study using neither randomisation nor controls prevents inferential ability, and it is acknowledged that further studies are required. The methodology employed may be useful in monitoring disease progression rates on patients treated with riluzole.

Kalra *et al* (1998)[49] used magnetic resonance spectroscopy to measure the N-acetylaspartate: creatine relative resonance intensity ratio (NAA/Cr) in the motor cortex, as a marker for neuronal loss. They reported that 11 patients treated with 100mg/day of riluzole for 3 weeks experienced an increase in NAA/Cr (indicating a reversal in corticomotor neuronal loss), compared to a decrease in 12 control patients. The study was non-randomised, using a small sample of patients and short follow-up times.

Gawel (1999, unpublished)[50] analysed 528 patients with ALS in a single-centre, non-randomised study using historical controls. The clinic was included in the Canadian early access riluzole program. Most patients with ALS presenting at the clinic since 1995 (n=159) were given 100mg/day of riluzole. Demographic characteristics were similar in both groups, except for the fact that a greater proportion of control group patients presented with spasticity. At 12 months, 89% of riluzole patients were still alive, compared to 87% of controls. At 18 months, 77% of riluzole patients were alive, compared with 70% of controls. These results show survival rates much higher than those reported by Bensimon *et al* (1994).[43] The author suggests this difference in results between studies may reflect the study design, as only newly diagnosed patients were included.

Arrida-Mendicoa *et al* (1999)[51] carried out an open-label, non-randomised, non-comparative study to evaluate the effect of 100mg/day of riluzole on clinical progression, in 50 Mexican patients with ALS. Patients were assessed using the Jablecki scale. 31 patients completed the one-year study. At the end of the study, monthly progression of the disease had decreased significantly both for bulbar and limb onset. No severe side effects were recorded. The authors conclude that riluzole can delay disease progression, and should be considered for ALS patients. They recommend making it clear that ALS cannot be cured, and that economic issues should be taken into account.

Desiato *et al* (1999)[52] assessed 31 patients with ALS in a 6 month prospective open study, using single and paired transcranial magnetic stimulation (TMS). The study evaluated 31 patients with ALS receiving 100mg/day of riluzole, and 30 age-matched controls. A number of parameters were measured before and after the administration of riluzole. Significant differences were recorded between treated patients and controls in two parameters (normal behaviour of the silent period duration in response to increasing TMS of treated patients, and the size of motor evoked potential duration was significantly reduced in treated patients, compared with controls). The authors conclude that their assessment method may be considered a setting for controlled trials in extended patient series, even in a pre-clinical phase.

Pongratz *et al* (1999)[53] evaluated the safety of riluzole in an open-label, multi-national, uncontrolled trial. The study was conducted between 1995 and 1997, and each patient received 100mg/day of riluzole for a mean of 7.2 months. A total of 7,916 patients with ALS in 39 countries participated, though the paper concentrates on the 919 patients treated in Germany. 17.6 % of German patients died from ALS during the study. The most frequent adverse events were reduced lung function (7.1%), asthenia (5.8%), pneumonia (2.5%) and abdominal pain (2.5%). Serious adverse events attributed to riluzole occurred in 16 patients (1.7%), most of which were changes in liver enzyme, which were reversible and non-fatal. The authors conclude that riluzole is well tolerated.

Most adverse events were due to symptoms of ALS. Observed adverse events were lower than those reported in previous studies. The safety profile from the German centres was similar to the total study population.

Couratier *et al* (2000)[54] published a cohort study describing part of the content of a computerised database for patients with ALS. A total of 340 patients were studied, 159 of whom were treated with riluzole. Median survival for riluzole patients was 52 months.

Appendix 7 - Survival data extraction

The appropriate summary statistic for use with survival (time to event) data is the hazard ratio, which summarises the difference between two Kaplan-Meier survival curves and represents the overall relative risk of death over the period of follow-up of patients. This is preferable to simple comparisons of the overall number of events or the odds of survival at fixed timepoints.[79]

In order to combine survival data from different trials, an estimate of the log hazard ratio and it's variance for each trial is needed.

The pooled hazard ratio (HR) and associated 95% confidence interval are calculated (using the fixed effects model) as follows:

$$\ln(HR) = \frac{\sum\left(\frac{\ln(HR_i)}{Var[\ln(HR_i)]}\right)}{\sum\left(\frac{1}{Var[\ln(HR_i)]}\right)}$$

$$Var[\ln(HR)] = \frac{1}{\sum\left(\frac{1}{Var[\ln(HR_i)]}\right)}$$

The pooled hazard ratio and associated 95% confidence interval are given by

$$\exp\left\{\ln(HR) \pm 1.96\sqrt{Var[\ln(HR)]}\right\}$$

Information available from trial reports

Although the log hazard ratio and it's variance are rarely reported directly, these may be estimated from the hazard ratio and an associated 100(1-α)% confidence interval as follows:[79]

$$Var[\ln(HR)] = \left(\frac{\ln(UppCI) - \ln(LowCI)}{2 \times z_{(1-a/2)}}\right)^2$$

Estimating the hazard ratio where it is not reported

Where no estimate of the hazard ratio or the uncertainty surrounding this estimate is given, methods are available to estimate these from the published Kaplan-Meier survival curves.[79] However, in this case all of the survival curves in each of the trial reports were accompanied by a summary of the number of patients 'at risk' (i.e. still alive and with follow-up) at the start of each three month interval (up to 18 or 21 months) and the number of patients dying within each of these intervals. The numbers censored (known to be alive at last follow-up) within each interval may thus be calculated. We have used these figures to estimate summary survival statistics using the usual logrank method and the Mantel-Haenszel estimates of the log hazard ratio and it's variance.

The logrank method accounts for censoring between but not within intervals, i.e. it assumes that individuals who are censored at a particular time point lived longer than individuals who died at the same time point. For this assumption to be reasonable, the raw data should be recorded in 'short' time intervals (e.g. hour, day or month of death, depending on the context). In this case, we are not analysing raw data, but rather we are trying to approximate the raw (individual patient) data from these trials using the summary information given with the Kaplan-Meier survival curves. In using the usual logrank method, we are effectively assuming that, in the original data sets, all patients censored within each 3 month interval were censored at the end of the interval, whilst all the deaths within the interval occurred at some earlier point in the interval. Clearly this assumption may not accurately reflect the original data set. Thus, in order to investigate the reliability of this method, we performed the calculation for all Kaplan-Meier summary data presented in each trial, even where the hazard ratio and a 95% confidence interval were adequately reported; where data are available from both sources, the estimates may be compared. Our estimates, along with the data available from the trial reports, are summarised in Appendix 8 on page 63.

Despite using summary data at 3 month intervals, where we have data available from both sources our estimates seem to be reasonably consistent with the published information. We are not aware of any methodological literature on an 'actuarial' approach to the logrank method where time intervals are 'long', but we also examined estimates derived from a simple 'actuarial' approach (making some allowance for censoring within intervals). Where they differed to any degree, these estimates tended to perform rather worse than those derived without any allowance for censoring within intervals. This may be due to the particular trials included here. The common approach in these trials seems to have been to follow-up patients for a specified period of time (18 months) rather than to follow-up all patients until an event is observed. All of the trials report very little loss of follow-up prior to 15 months. Under these circumstances a simple adjustment which assumes that censoring is uniform through the interval may over-compensate for heavy censoring within the last two intervals. Whatever the reason, the usual logrank approach seems to work well for this group of trials, although it might be less reliable for trials with a different pattern of follow-up.

The results presented in Section 4 are those presented directly in the trial report where available; estimates derived from the Kaplan-Meier summary data are used where the information is not directly available from the trial report.

Appendix 8 - Results (reported and estimated) from each trial

Survival results, reported directly by the authors or estimated from the Kaplan-Meier summary data (see Appendix 7 on page 61) are summarised in Figures A8.1-A8.4 below. For each result we have summarised data available directly from the trial report ('reported') and data estimated from the Kaplan-Meier summary data ('estimated'); in some cases only a (logrank) p-value is available from the trial reports and these are included for comparison. The reported/estimated pairs are plotted adjacent to each other on the figures to facilitate comparison where data is available by both means.

Adjusted estimates derived from the Cox model are also summarised on these plots. The covariates included in the adjusted models are listed in Table A8.1 below.

Figure A8.1 Bensimon *et al.*

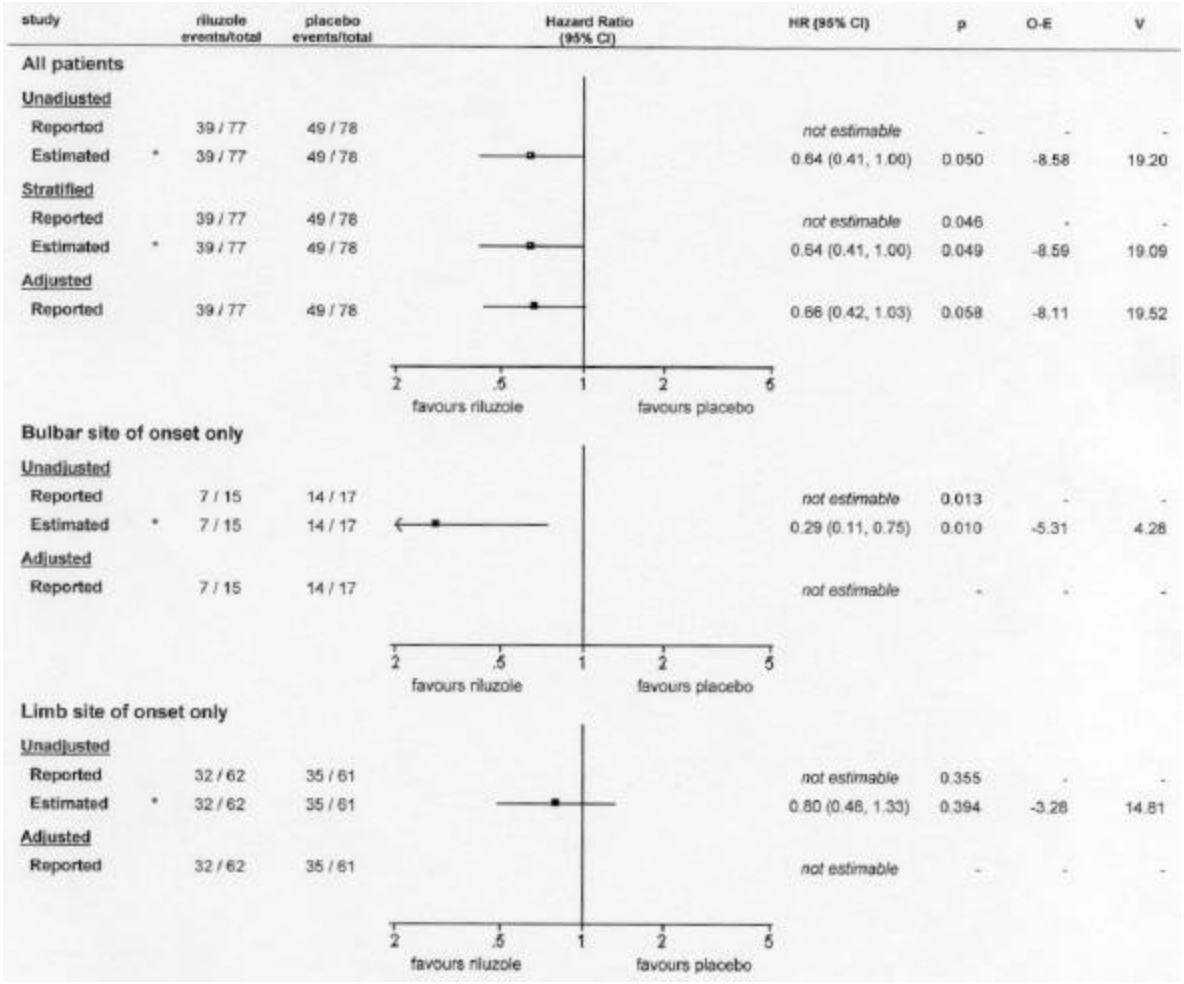
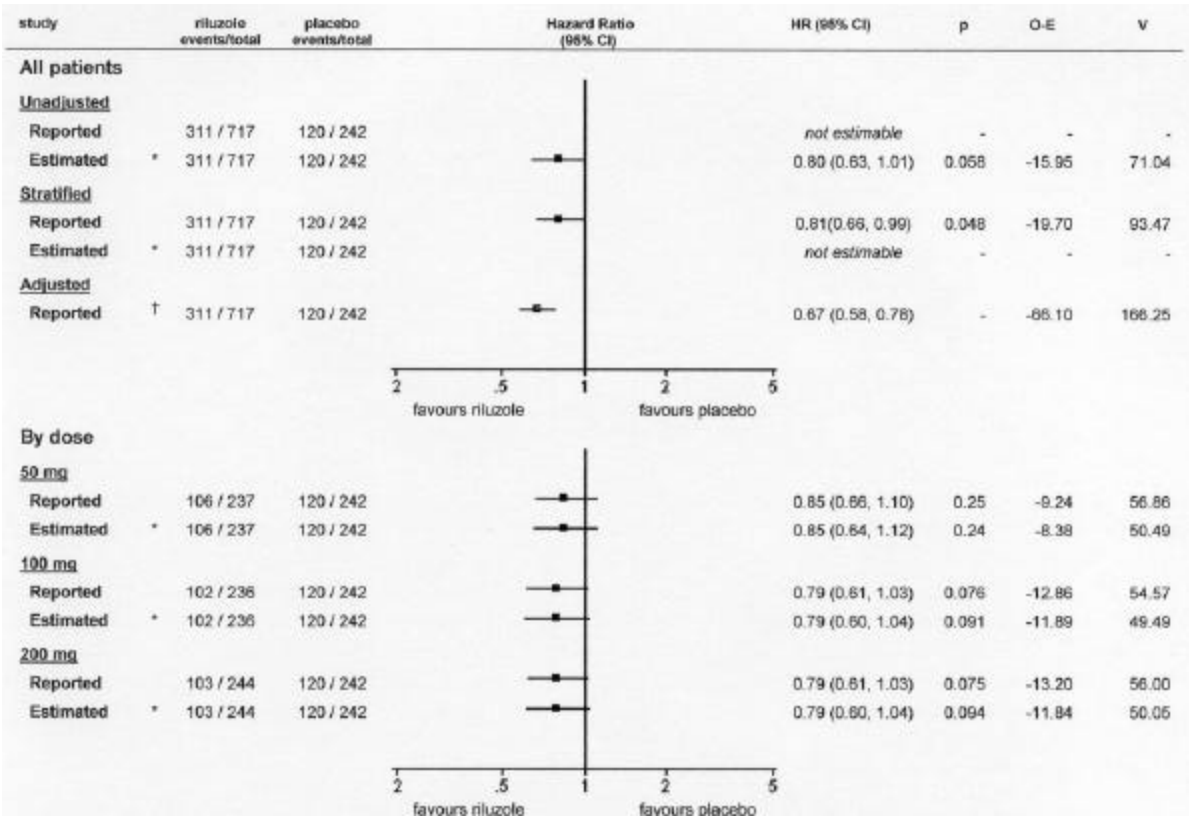


Figure A8.2 Lacomblez *et al.*



† adjusted results reported for each riluzole arm separately; results presented here are stratified pooled results for all riluzole arms combined

Figure A8.3 Meininger *et al.*

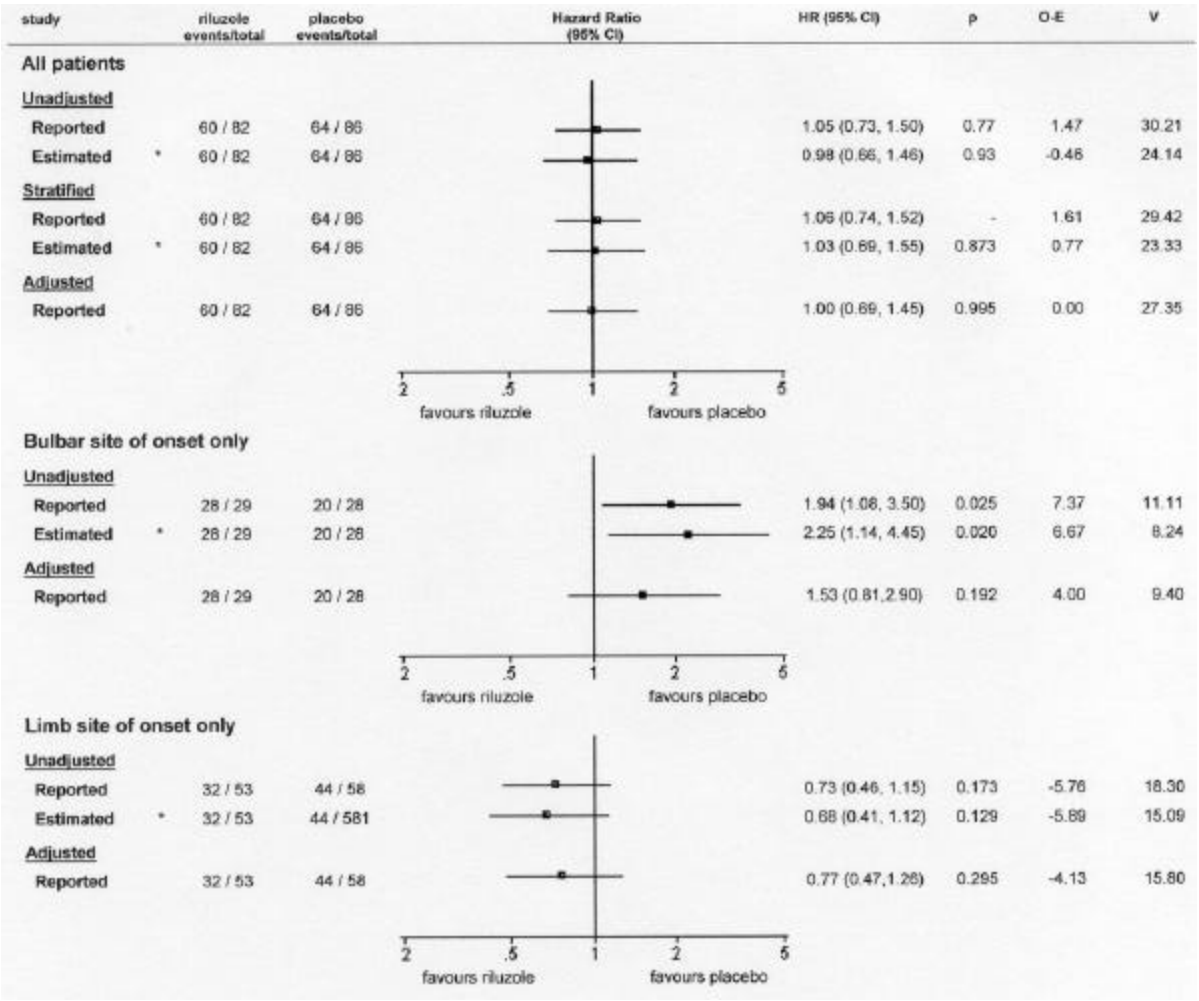


Figure A8.4 Yanagisawa et al. (progression-free survival)

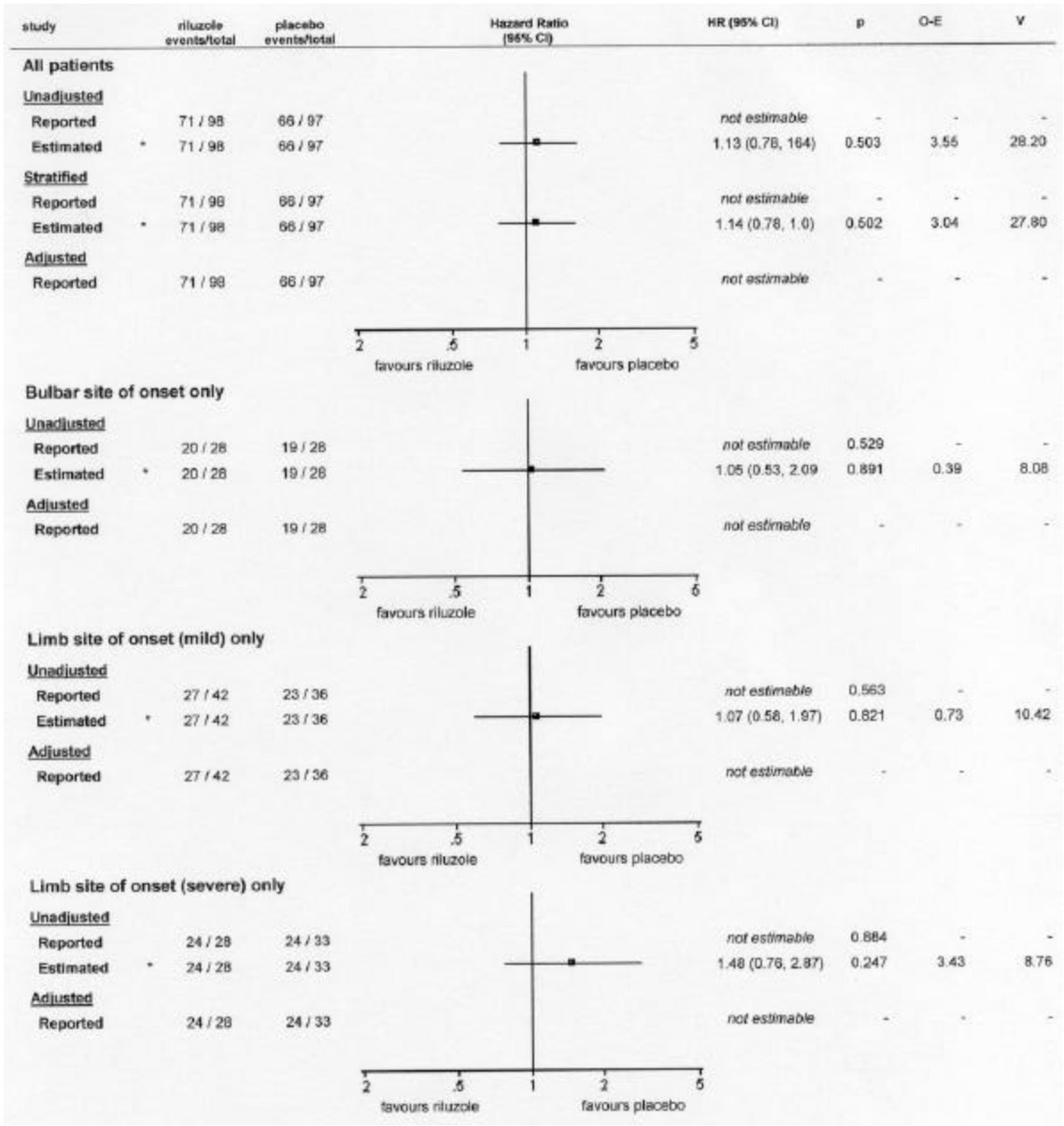


Table A8.1 Covariates included in the Cox regression models for each trial

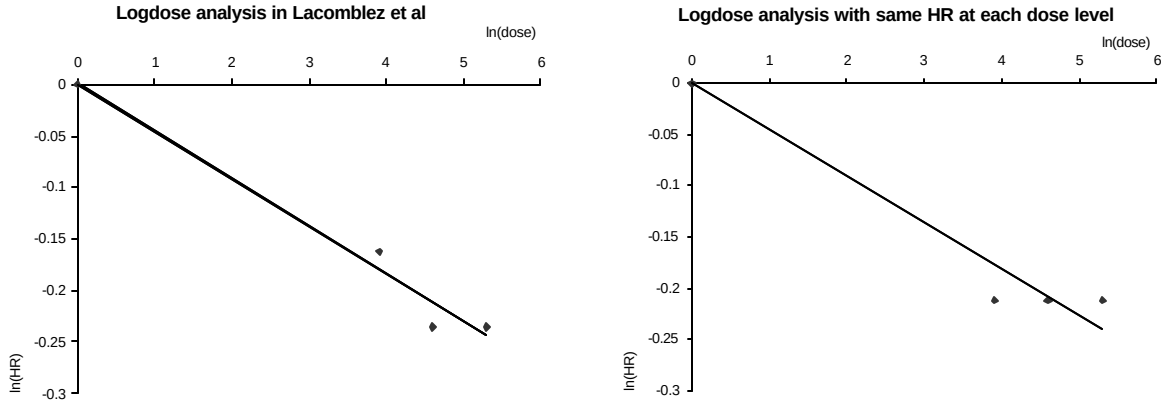
Covariates	Bensimon	Lacomblez	Meininger	Yanagisawa
Stratified by site	**yes**	**yes**	**yes**	?
age	**yes**	**yes**	**yes**	*not stated*
vital capacity	**yes**	**yes**	**yes**	*not stated*
duration of disease	**yes**	**yes**	**yes**	*not stated*
bulbar function	**yes**	no	no	*not stated*
stiffness scale	**yes**	**yes**	**yes**	*not stated*
tiredness scale	**yes**	**yes**	**yes**	*not stated*
bulbar signs	no	**yes**	no	*not stated*
weight	no	**yes**	no	*not stated*
muscle testing	no	**yes**	**yes**	*not stated*
CGI severity	no	**yes**	no	*not stated*
country grouping	no	**yes**	no	*not stated*
VAS fasciculations	no	no	**yes**	*not stated*
heart rate	no	no	**yes**	*not stated*

Appendix 9 - Doses used in Lacomblez trial

The Lacomblez trial used three different doses of Riluzole, 50mg, 100mg and 200mg. The results for each of these arms are summarised in Figure A8.2 (see Appendix 8, on page 63). There is no indication of any difference in effectiveness between these different dose levels; a much larger trial would be required in order to detect any modest trend in outcome due to the dose used.

The authors of this trial do claim to have found a positive relationship between dose and outcome, but it is not clear that this is an appropriate interpretation of the model they used. The claim is based on fitting 'logdose' in the Cox proportional hazards model, replacing the undefined log of zero (placebo) with zero (the log of 1). No clear rationale is given by the authors for using 'logdose' instead of 'dose' in the model. This model is illustrated graphically below (Figure A9.1a).

Figure A9.1 (a,b) Logdose in the Cox proportional hazards model.



The slope of the 'best straight line' between these points, indicated in the figure, is the estimated change in log hazard ratio associated with a unit increase in the log of the dose. Lacomblez *et al* report this coefficient as significant, with a hazard ratio of 0.95 and 95% confidence interval of 0.91 to 0.99 (p=0.04). They appear to interpret this as evidence of a dose-outcome relationship. However, the significance of the slope is due to the presence of a drug effect, not the existence of a dose response relationship. Even if the estimated hazard ratios at each dose level were identical then this analysis would find a significant slope, as long as the common hazard ratio was large enough compared to the error in the model (see Figure A9.1b). The log transformation exaggerates the significance of the slope in both models (by altering the position of the observations relative to each other and to placebo on the x axis compared to the untransformed values of 0, 50, 100 and 200), but there is little difference between the two alternatives, as can be seen from the figures.

In order to demonstrate a relationship between dose and outcome, it is necessary to show that a model which contains information on the dose level clearly fits (or 'explains') the data better than one which merely regards active treatment as present or absent (regardless of the dose used). There is no evidence of any trend in outcome by dose level in the data presented by Lacomblez *et al.* Estimates for all dose levels combined from this trial have therefore been used in the main body of this report.

Appendix 10 - Comment on meta-analysis in EPAR report

In the course of this review, an European Public Assessment Report for the European Medicines Evaluation Agency was found which made some reference to an individual patient data meta-analysis of the four RCTs included in the review. Further information about this meta-analysis was sought from Aventis. These data were not made available in time for inclusion in this appraisal report and are thus submitted here as a separate addendum with some brief comments as follows.

Data made available

The attached report summarises the results of a meta-analysis performed by Rhône-Poulenc Rorer based on individual patient data from studies 216 ["Bensimon *et al*" in our review], 301 ["Lacomblez *et al*"], 302 ["Meininger *et al*"] and 304 ["Yanagisawa *et al*"]. Data on riluzole at 50mg and 200mg from the Lacomblez trial are not included. The report summarises the endpoint of tracheostomy-free survival, as given in each of the trial reports and, in addition, gives data on overall survival.

Of particular interest here are the results of the Yanagisawa trial [study 304], as no numerical results were available from the trial report and thus this trial could not be combined with the others in our review.

Results of a cluster analysis are also summarised, although it is not clear why this analysis was performed or how these data might be interpreted.

Results

The Inclusion of the Yanagisawa data, as expected, shifts the results for tracheostomy-free survival towards the null; estimated hazard ratio 0.89 (0.75-1.05) compared to our estimate of 0.83 (0.69-0.99). The differences between these results are of no practical importance; the upper limit of the CI is still compatible with little or no benefit. However, the impression of heterogeneity, noted in the review, is strengthened, with a p-value for heterogeneity of 0.09 (compared to 0.39 previously).

[We have repeated this analysis including the data from 50mg and 200mg arms of Lacomblez *et al*; the results are very similar, with an estimated hazard ratio of 0.88 (0.75, 1.02) and p-value for heterogeneity of 0.09].

Results for overall survival, which have not been reported elsewhere, are similar to those for tracheostomy-free survival.

Results obtained using the Cox Proportional Hazards Model are also summarised; these do not substantially alter the conclusions. Some missing data were imputed for these analyses; it is not possible to assess what influence this may have had.

Results of a cluster analysis are also summarised. It is not clear that cluster analysis of this type is useful for identifying meaningful subgroups of patients across a large number of variables; not surprisingly the two groups identified in this way do not differ as much with respect to prognosis as the 'high risk' and 'low risk' groups identified by Lacomblez *et al* and by Yanagisawa *et al* using prognostic indices derived from the Cox model. There are a number of problems with the application and interpretation of the cluster technique used here, although more detailed information would be needed for a full critique. It is worth noting that the most influential variables in forming the clusters were FEV and VC; no mention is made of standardised scores being used in the analysis, and so the influential nature of these two variables may be due simply to the fact that they have the greatest range (in absolute terms) and will thus dominate the analysis regardless of any underlying structure. Furthermore, it is noted on page 3 of the report that respiratory function was not assessable in large numbers of patients in study 302 (Meininger *et al*) and that for analysis these patients were assigned the minimum values of FEV and VC observed for other patients in the study; this will clearly lead to some spurious 'clustering' based on these variables and, given the importance of these variables in the procedure, would distort the cluster assignment. The results of the cluster analysis, as presented, are uninterpretable.

Implications of the new data

The results for tracheostomy-free survival using full data from all four trials do not differ markedly from the results we obtained using data from only three of the trials; there is still weak evidence of a small difference in tracheostomy-free survival favouring riluzole, although this evidence is now rather less convincing.

However, results of the fourth trial are somewhat in favour of placebo and inclusion of these data increases the impression of heterogeneity between these trials. Whilst the trial by Meininger *et al* clearly did recruit a very different patient population from the other three trials, the patient characteristics in the other trials appear very similar with the only clear difference being European vs Japanese settings. There is no clear explanation for the apparent heterogeneity in the results of these trials and the pooled result should therefore be treated with some caution. If the apparent heterogeneity is *not* due to chance but rather due to differences between the trials, then we cannot assess the 'true' benefit of riluzole without understanding why these trials differ; if the apparent heterogeneity *is* due to chance, then the pooled estimate given here is the most reliable estimate currently available.

The economic evaluation of riluzole presented in the systematic review employed the most favourable scenario for riluzole, that is the results of the trials by Bensimon *et al* and Lacomblez *et al* combined. This is still the most favourable scenario for riluzole. Inclusion of the data from the trial by Yanagisawa *et al* would clearly not improve the cost effectiveness of riluzole.

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