# Cost Effectiveness Analysis of Riluzole for ALS in Ontario Home Care Setting

**by**

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# AUTHOR'S DECLARATION

I hereby declare that I am the sole author of this thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

I understand that my thesis may be made electronically available to the public.

# ABSTRACT

**Objective:** To identify the factors associated with the prescription of riluzole and assess its cost-effectiveness for patients diagnosed with Amyotrophic Lateral Sclerosis (ALS) in long stay home care in Ontario, Canada.

**Method:** A retrospective cohort study was conducted using the Ontario Association of Community Care Access Centres – Home Care (OACCAC-HC) data. Assessment records of ALS patients admitted into home care between April 1st, 2005 and March 31st, 2013, who had information on whether or not they used riluzole, were reviewed. Univariate and multiple logistic regressions analysis were used to identify the predictors influencing the receipt of riluzole. Variables included in the analyses were chosen in correlation to the prognostic factors identified in the literature review. For the cost-effectiveness analysis, cost data were obtained from relevant literatures and published information on Canadian Institute for Health Information Patient Cost Estimator accounting for the cost of administration of riluzole, standard supportive home care services, and cost-savings from delay in hospitalization. Effectiveness was measured using time to discharge from home care due to death, placement into long-term care, and hospitalization, controlling for potential confounding variables using propensity score stratification. The incremental cost-effectiveness ratio was calculated based on time spent in different states and the associated utility scores using the stratified population and expressed as cost per life-year gained and quality-adjusted life-year gained. Sensitivity analyses included one-way deterministic sensitivity analysis to investigate the change in ICER due to variations in specific input parameters. Scenario analyses were developed to depict the ICERs in best and worst case scenarios.

**Resuts:** The total study population comprised of 1,351 patients diagnosed with ALS, of which 1,277 patients had information on the use of riluzole. In the multiple logistic regression analysis, older age, moderate – moderate severe impairment in cognitive functions, not being married and geographical locations across LHINs (Champlain, Erie St. Clair, Hamilton Niagara Haldimand Brant, Mississauga Halton, North East, South East, and South West) decreased the likelihood of riluzole prescription. Primary analysis showed that treatment with riluzole was associated with prolonged survival in home care [HR = 0.86; 95% confidence interval: 0.745 – 0.99; p=0.046]. Survival gain associated with riluzole was 1.5 months, while the incremental cost was approximately $5,000 per patient. Thus, the incremental cost-effectiveness ratio of riluzole versus standard supportive home care services was $41,128.85 per life-year gained or $55,579.53 per quality-adjusted life-year gained. One-way deterministic sensitivity analysis suggested an ICER ranging from $50,000 – 78,000 per QALY, while scenario analyses depicting best and worst case scenarios suggested an ICERs of $29,890.36 per QALY and $106,641.52 per QALY.

**Conclusion:** Patient characteristics such as age, cognitive score, geographical location and marital status markedly influenced drug utilization of riluzole. In addition, the findings of this

study indicate that riluzole has a borderline or unfavorable cost-effectiveness for patients diagnosed with ALS in home care setting.

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## LIST OF ABBREVIATIONS

| ABBREVIATIONS | FULL TEXT |
|---|---|
| **ADL** | Activities of Daily Living |
| **ALS** | Amyotrophic Lateral Sclerosis |
| **CCC** | Complex Continuing Care |
| **CEA** | Cost-Effectiveness Analysis |
| **CHESS** | Changes in Health, End-Stage, Signs and Symptoms |
| **CI** | Confidence Interval |
| **CIHI** | Canadian Institute for Health Information |
| **CPI** | Consumer Price Index |
| **CPS** | Cognitive Performance Scale |
| **DALY** | Disability-Adjusted Life Year |
| **DRS** | Depression Rating Scale |
| **FDA** | Food and Drug Administration |
| **HC** | Home Care |
| **HR** | Hazard Ratio |
| **IADL** | Instrumental Activities of Daily Living |
| **ICER** | Incremental Cost Effectiveness Ratio |
| **LHIN** | Local Health Integration Network |
| **LTC** | Long-Term Care |
| **LYG** | Life Year Gained |
| **MAPLE** | Methods for Assigning Priority Levels |
| **MOHLTC** | Ministry of Health and Long Term Care |
| **NH** | Nursing Home |
| **OACCAC** | Ontario Association of Community Care Access Centres |
| **OR** | Odds Ratio |
| **PCE** | Patient Cost Estimator |
| **QALY** | Quality-Adjusted Life Year |
| **RAI** | Resident Assessment Instrument |
| **PC** | Palliative Care |

## Chapter 1: Introduction

Amyotrophic Lateral Sclerosis (ALS) is a chronic degenerative disease involving upper and lower motor neurons with no known etiology (Klein & Forshew, 1996). The progressive loss of muscle strength and pulmonary function eventually leads to death, which is most commonly caused by respiratory muscle failure (Ginsberg & Lowe, 2002). The survival time can vary significantly between individuals; however, an average survival time is between 2 to 5 years after initial diagnosis (Radunovic, Annane, Jewitt, & Mustfa, 2010).

Currently, riluzole is the only approved medication to treat ALS. Despite its modest survival benefits, the drug is known to represent a significant economic burden for patients and caregivers. Cost-effectiveness studies have attempted to identify factors driving the costs of treatment along with measurement of survival benefits associated with riluzole, however, lack of long-term data have limited the accuracy of stage-specific cost and survival estimates within different care settings (Home Care, Nursing Home, Complex Continuing Care). Based on the length of stay in different care facilities, the costs involved in the overall treatment as well as the quality of life of patients can significantly differ. As riluzole is known to prolong and maintain patients' health status in mild to moderate stage (Bensimon & Lacomblez & Meininger, 1994), it is important to accurately assess the delays in transitions to other care settings in order to fully understand how the drug affects the cost of care as well as the quality-of-life in ALS patients.

Using Ontario Association of Community Care Access Centres – Home Care (OACCAC-HC) assessments, which collects person-level data on various demographic and clinical variables with discharge information, along with cost estimations derived from previous economic burden studies of ALS, this proposed study will contribute to previous findings by measuring survival benefits using observational data. It will also produce reliable

direct cost estimates associated with the use of riluzole to determine its cost-effectiveness specific to the Canadian context.

## Chapter 2: Literature Review

### 2.1 Overview of ALS

#### Clinical Features

Amyotrophic Lateral Sclerosis (ALS) is a progressive neurodegenerative disorder with no known etiology or cure (Klein & Forshew, 1996). ALS affects both upper and lower motor neurons in the brain and the spinal cord, causing progressive loss of voluntary motor activity (speech, swallowing, and respiratory function) and muscle weakness, which results in nearly all patients developing dysphagia, excessive salivation and weight loss (Ginsberg & Lowe, 2002). Eventually, patients will become dependent on others to carry out their daily activities, and ultimately may require enteral feeding, hospice care, tracheostomy, and mechanical ventilation in order to sustain life. Majority of deaths associated with ALS is due to respiratory failures, and death usually occurs within 2 to 5 years after onset of symptoms (Radunovic et al., 2010).

#### Classification

Epidemiological and genetic factors allow ALS to be classified into two categories. In approximately 90–95 percent of all ALS occurrences, the disease occurs at random with no associated risk factors (Kiernan et al., 2011). This form of ALS is classified as classical sporadic ALS. Patients with sporadic ALS have no family history of ALS, and their family members are not considered to be at risk of developing ALS throughout their lifetime (Kiernan et al., 2011).

On the other hand, approximately 5-10 percent of all ALS occurrences are inherited and thus classified as familial ALS. This form of ALS stems from a pattern of inheritance in which one parent carries the gene responsible for the disease (Kiernan et al., 2011). One third of all familial ALS and small percentage of sporadic ALS are linked to a defect in a gene known as "chromosome 9 open reading frame 72" or C9orf72 (Mizielinska & Isaacs, 2014). Moreover, 20 percent of all familial ALS incidences are linked to a mutation of copper zinc superoxide dismutase 1 (SOD1) in chromosome 21 (Siddique & Deng, 1996).

**Epidemiology**

ALS is most common for people aged between 40 to 75 years old (Miller et al, 2000). While the disease is relatively rare, it still affects thousands of people worldwide, with country-specific prevalence ranging from 1-10 cases per 100,000 population and average prevalence of 7/100,000 population worldwide (Ginsberg & Lowe, 2002). Crude incidence rate of ALS ranges between 0.3 and 2.6 cases per 100,000 population, with an average crude incidence of 1.75/100,000 population worldwide (Ginsberg & Lowe, 2002). It has been previously indicated that males are more vulnerable to ALS with an overall ratio of about 1.5 men to every woman (Tsai, Wang, Hwang, Lee, & Lee, 2015). Current trends suggest that incidence of ALS is increasing globally due to increases in longevity and improved diagnostic capabilities (Kahana & Zilber, 1984).

**Symptoms and Diagnosis**

As ALS is progressive in nature, symptoms and signs become more apparent as the disease progresses from the onset. There are 4 stages to ALS. As patients consecutively shift from one stage to another, symptoms gradually worsen altogether and ultimately result in death. Descriptions of stages of ALS along with the supportive care required in each stage

can be found in *Appendix A.* ALS patients may often require a comprehensive team of doctors and specialists to manage the symptoms. Specialists involved in the management of ALS might include: neurologists; physiatrists; nutritionists; gastroenterologists; occupational therapists; respiratory therapists; speech language therapists; social workers; infectious disease specialists; mental health professionals; nurses; personal support workers and an internist (Munsat, Riviere, Swash & Leclerc, 1998). Moreover, research suggests that the median duration of time spent in any stage was 10.9 months (95% CI 10.4 – 11.4) (Balendra et al., 2014).

There is no single laboratory test or procedure that could confirm the diagnosis of ALS. Hence, a series of clinical procedures and diagnostic tests are conducted to rule out other neurological diseases that do not conform to the symptoms of ALS (Chio, 1999). Comprehensive diagnostic tests include, but are not limited to: electromyography (EMG), nerve conduction study (NCS), spinal tap, X-rays, magnetic resonance imaging (MRI), muscle biopsy, genetic tests, and blood and urine tests (Klein & Forshew, 1996)

**Medication**

Riluzole (6-(trifluoromethoxy) benzothiazol-2-amine) is the only FDA-approved drug for the treatment of ALS (Messori et al., 1999). First developed as an antiepileptic agent by Rhône-Poulenc Rorer in France, the drug currently has no other indication except than for the treatment for ALS. As part of the class of antiglutamates, riluzole works by inhibiting the release of a compound called glutamate that is known to injure nerve cells (Ginsberg & Lowe, 2002). Riluzole will not fully cure ALS; however, it can prolong life and delay the need for tracheostomy or ventilator-dependence (Ginsberg & Lowe, 2002; Gray, 1998; Messori et al., 1999).

Riluzole (Rilutek®) was first approved by The Food and Drug Administration (FDA)

in 1995, and since then, Rilutek has been used to treat ALS for nearly 20 years (full summary of history of Rilutek® can be found in *Appendix B*). Results from the double-blind, placebo-controlled efficacy trials of riluzole showed that use of riluzole (100mg daily) provides only moderate survival effect and prolongs life by approximately two months (Lacomblez, Bensimon, Meininger, Leigh & Guillet, 1996; Miller, Mitchell, Lyon & Moore, 2003). The results indicate that patients treated with riluzole remained in moderate health state longer than patients treated with placebo, and significantly slowed down the deterioration of muscle strength (Bensimon et al., 1994). A summary of the two randomized clinical trials of riluzole is shown in *Table 1*.

It has been recommended that patients receive an initial dosage of 50 mg/day and after a week, the dosage should be increased to 100 mg/day (50 mg every morning and evening) on an empty stomach (Ginsberg & Lowe, 2002). Studies have found that 100 mg/day delivered optimal results, while increasing the dosage to 200 mg/day had no additional benefits (Ginsberg & Lowe, 2002; Gray, 1998).

Previous research suggests that riluzole is more effective in the earlier stages of ALS, with bulbar-onset patients having more beneficial effects than limb-onset patients (Zoccolella et al., 2007). Moreover, patients over the age of 70 years old who were prescribed to riluzole had 8 months longer median survival time and reduction in mortality rate at 12 months by 27%, regardless of site of symptom onset (Zoccolella et al., 2007).

To date, no study has investigated the prevalence of use of riluzole, specifically in home care setting. Furthermore, the drug utilization of riluzole, as well as characteristics determining the prescription candidacy of riluzole remains poorly understood.

**Table 1: Summary of randomized clinical trials of Riluzole**

| Author(s) | Year | Country | Inclusion Criteria | Results |
|---|---|---|---|---|
| Bensimon, Lacomblez & Meininger | 1994 | France, Belgium | **n = 155**<br>**Age:** 20 - 75 years old<br>**Forced Vital Capacity (FVC):** ≥ 60%<br>**Duration:** ≤ 5 years of disease onset<br>**Clinical signs:** Excluded if patients had signs of conduction blocks of motor nerves, sensory nerves, paraproteinemia on immunoelectrophoresis, lesions for clinical signs on CT or MRI, and dementia. Moreover, those who underwent tracheostomy, had hepatic or renal dysfunction or if they were pregnant were also excluded. | **1.** 0-9 months: Improved survival rates in bulbar-onset patients taking riluzole<br>**2.** 9-18 months: No difference in survival rates for both treatment & placebo group<br>**3.** After 12 months, 45/78 in the placebo group were still alive, as compared with 57/77 patients in riluzole group.<br>**4.** Bulbar-onset patients: One year survival rates were 35% with placebo group and 73% with riluzole group.<br>**5.** Limb-onset patients: One year survival rates were 64% with placebo group and 74% with riluzole group.<br>**6.** Deterioration of muscle strength was significantly slower in the riluzole group |
| Lacomblez, Bensimon, Meininger, Leigh & Guillet | 1996 | Belgium, Canada, France, Germany, Spain, UK, USA | **n = 959**<br>**Age:** 18 - 75 years old<br>**Forced Vital Capacity (FVC):** ≥ 60%<br>**Duration:** ≤ 5 years of disease onset<br>**Clinical signs:** Patients with tracheostomy, renal dysfunction, other life-threatening disease, and pregnant women were excluded | **1.** At 18 months, 122 (50.4%) of placebo group and 134 (56.8%) of riluzole 100 mg/day group were still alive without tracheostomy (adjusted risk = 0.65). 131 (55.3%) of riluzole 50 mg/day group and 141 (57.8%) of riluzole 200 mg/day group were still alive without tracheostomy (adjusted risk for 50mg = 0.76; adjusted risk for 200mg = 0.61).<br>**2.** At 18 months, the 50mg, 100mg, and 200mg riluzole doses decreased the risk of death or tracheostomy by 24%, 35% and 39% respectively.<br>**3.** There were no reported difference in treatment effects between groups with different site of symptom onset or in groups of countries<br>**4.** 100mg dose of riluzole per day had the best benefit-to-risk ratio |

## 2.2 Prognostic Factors

### 2.2.1 Demographic Factors

#### Age

Majority of studies have found that age at the time of diagnosis or symptom onset is a major prognostic factor in ALS, with decrease in survival time in correlation to increase in age (Louwerse, Visser, Bossuyt, & Weverling, 1997; Preux et al., 1996; Stambler, Charatan & Cedarbaum, 1998; Testa, Lovati, Ferrarini, Salmoiraghi & Filippini, 2004; Uebayashi, Yase, Tanaka, Shimada & Toyokura, 1984). A diagnosis of ALS at younger ages is associated with longer survival and slower disease progression, even after adjustments for possible confounding factors associated with age (Czaplinski, Yen & Appel; 2006; Czaplinski, Yen, Simpson & Appel, 2007). Patients diagnosed before 40 years of age have a median survival time of 6.01 years (95% CI 4.67-7.34), often surviving over 10 years, compared with median survival time of 3.23 years (95% CI 3.03-3.43) for patients diagnosed between 40 and 70 years old and 2.85 years (95% CI 2.47-3.23) for patients over 70 years old (Czaplinski et al., 2006). Mechanisms behind disease progression rate and survival time associated with age are unknown.

#### Gender

Previous studies have identified that there is no association between gender and prognosis (Czaplinski et al., 2006; McCombe & Henderson, 2010). While male patients have a greater likelihood of developing symptom onsets in the spinal regions whereas female patients tend to develop symptom onsets in the bulbar region, gender had no clear effect on survival (McCombe & Henderson, 2010). This finding is odd considering that majority of patients diagnosed with ALS are males (approximately 60%). However, some investigators

have found that shorter survival time was observed among women (Aguila, Longstreth, McGuire, Koepsell & Belle, 2003).

**Psychosocial Factors**

Psychosocial factors are important prognostic factors that have direct relationship with quality of life and survival in ALS patients. A longitudinal study that assessed 10 psychometric variables (hopelessness, depression, loneliness, perceived stress, anger expression, purpose-in-life, locus of control, life rating, social support, coping methods) observed that survival curves were significantly different between high and low psychological score groups (McDonald, Wiedenfeld, Hillel, Carpenter & Walter, 1994). Research suggests that patients with psychological distress have a 6.76-fold increased risk of mortality and a 2.24-fold increased risk of dying in any given time period in comparison to patients with psychological well-being (McDonald et al., 1994). Moreover, a cross-sectional study assessing the determinants of quality of life in ALS patients has found that quality of life associated with ALS is not dependent upon one's physical status, but rather relies mainly on psychological and supportive factors (Chio et al., 2004). Therefore, it is important for clinicians not to overlook psychological factors and thereby provide structured psychosocial interventions to both patients and caregivers in order to improve quality of life and survival in the course of the disease management.

### 2.2.2 Clinical Factors

**Site of Onset**

ALS is usually manifested through weakness in upper limb, lower limb, or bulbar musculature. In 75-80% of patients, symptoms begin with weakness in limb involvement (limb-onset patients), while 20-25% of patients begin with difficulty swallowing or eating

due to weakness of the tongue or pharyngeal muscles (bulbar-onset patients) (Turner et al., 2009).

Previous studies have reported that disease onset in the bulbar muscles is associated with shorter survival time in comparison to limb/spinal onset (3.74 years vs 2.80 years, $p<0.001$) (Czaplinski et al., 2006; Testa et al., 2004; Uebayashi et al., 1984). Bulbar-onset patients have faster decline rate of respiratory functions, malnutrition, and dehydration (Louwerse et al., 1997). Bulbar symptoms are an independent prognostic factor, which indicates that presence of bulbar functions at any point of the disease is a predictive factor of shorter survival outcome. On the other hand, patients with limb symptoms at onset have slower disease progression and longer survival (Czaplinski et al., 2006; Stambler et al., 1998). Within limb symptoms, research suggests that lower limb onset is associated with poorer prognosis due to an increased risk of thromboembolic disease and infections from declined rate of motility in comparison to upper limb onset (Preux et al., 1996; Uebayashi et al., 1984). However, one study has identified that poorer prognosis was observed among patients with upper limb onset (Magnus et al., 2002). While it is clear that bulbar-onset patients have shorter survival than limb-onset patients, more research on limb-onset patients is necessary in order to fully understand the prognostic effects in lower and upper limb onsets.

**Delay in Diagnosis**

The time delay between symptom onset and first diagnosis was a strong indicator of a better prognosis. The delay is negatively related to hazard, meaning that the longer the delay, the longer the survival and the slower the disease progression (Aguila et al., 2003; Haverkamp, Appel & Appel, 1995; Stambler et al., 1998). While exact association is unknown, investigators have suggested that time between symptom onset and first diagnosis is likely to indicate the initial rate of disease progression, meaning short time delay is likely

to indicate a more aggressive disease that requires more rapid medical attention whereas patients with slower disease progression are accustomed to initial symptoms for longer period of time before they seek medical care (Aguila et al., 2003; Haverkamp et al., 1995; Lee, Annegers & Appel, 1995).

**Cognitive Functions**

Patients and their caregivers are often told that ALS has no association with one's cognition; however, recent findings suggest that ALS patients develop progressive cognitive impairments (Lomen-Hoerth et al., 2003; Ringholz et al., 2005; Strong et al., 1999). Previous research suggests that cognitive impairments are present in 50% of all ALS patients and implicate executive dysfunction and mild memory decline during the disease progression (Laird, Studenski, Perera & Wallace, 2001). Approximately 5-10% of ALS patients develop frontotemporal lobar dementia (FTLD), and half of all patients have deficits in temporal and frontal executive functions (Lomen-Hoerth et al., 2003). Moreover, it has been found that bulbar-onset ALS patients with cognitive impairments developed greater severity of neuropsychological dysfunctions (Ringholz et al., 2005; Strong et al., 1999). One study has also found that ALS patients with FTLD have shorter survival than those without executive function deficits (Armon & Brandstater, 1999). While exact reasons are unknown, it is hypothesized that patients with FTLD have poor compliance with mechanical ventilation and percutaneous endoscopic gastrostomy (PEG) (Chio et al., 2012; Olney et al., 2005).

**Respiratory Functions**

As most deaths with ALS are associated with respiratory failure, respiratory function is an important determinant of outcome in patients with ALS. Conditions such as sleep disruption, hypopneas, orthopnea, and REM-related desaturation are common with declining

strengths of respiratory muscles (Bourke, Shaw & Gibson, 2001). Research suggests that forced vital capacity (FVC %) at the time of initial diagnosis was the most relevant predictor of outcome in ALS (Chio et al., 2002; Czaplinski et al., 2006; Stambler et al., 1998). Predicted vital capacity (VC %) and decline of VC % has shown to be correlated with overall survival time of patients (Chio et al., 2002; Czaplinski et al., 2006; Lyall, Donaldson, Polkey, Leigh & Moxham, 2001). Moreover, non-invasive sniff nasal pressure (SNP) has greatest predictive power, as it can accurately assess respiratory muscle strengths and its corresponding likelihood of ventilatory failure, but not for patients with significant bulbar involvement (Lyall et al., 2001).

**Nutrition**

The occurrence of malnutrition in patients with ALS is an independent prognostic factor and is significantly correlated with worsened survival (Desport et al., 1999; Desport et al., 2000). Malnutrition is primarily caused by swallowing dysfunction due to involvement of the lower sets of cranial nerves and is present in 16-50% of ALS patients (Desport et al., 2000). Nutrition status is assessed by calculating Body Mass Index (BMI) and BMI below 18.5-20 $kg/m^2$ indicates status of malnutrition (Desport et al., 2000). A prospective study assessing nutrition status and survival indicates that survival was worse for malnourished patients, with a 7.7-fold increased risk of death (Desport et al., 1999). Hence, constant nutritional surveillance and dietary counselling is necessary for optimal management of the disease.

**Falls**

Falls are independent predictors of adverse outcomes in ALS (Gil et al., 2008). Previous research suggests that approximately 2% of all deaths in ALS patients are falls

related (Rubenstein & Josephson, 2002). Previous research has identified numerous risk factors associated with falls such as muscle weakness, deficits in balance, visual deficits, arthritis, impairments in ADLs, signs of depression, and cognitive impairment (Ringholz et al., 2005).

### 2.3 Economic Impact of ALS

For the purpose of convenient comparison of economic impacts associated with ALS, all costs mentioned in this section have been converted to US currency rate as of September 2016 to adjust for inflation, and using US Inflation Calculator published by the latest US government Consumer Price Index (CPI) data.

#### Cost of Illness

In the US, *Larkindale et al*. estimated the total annual per-patient costs to be $63,693 for patients with ALS. The estimated costs are associated with direct medical, nonmedical, and indirect costs. Using Medicare claims data to estimate direct medical costs and cost-of-illness survey to estimate nonmedical costs and indirect family income loss, the study estimated $32,148 for annual direct costs, $18,479 for nonmedical costs and $15,166 for indirect family income loss. The study identified that ALS patient costs are significantly associated with use of wheelchairs and mechanical ventilators.

The costs estimated by *Larkindale et al*., are higher than those estimated by *Klein & Forshew.,* who estimated the costs of diagnosing ALS as between $15,338 to $30,675 depending on the types of procedures such as laboratory tests, electrophysiology, neuroimaging, and neuropathology. Moreover, augmentative communication equipment varied greatly in costs, ranging from $38 for an eye-blink board to $30,675 for computer system with ALS-specific software. Total cost per year for nutritional maintenance costs were

estimated to be $9,200 excluding PEG tube surgery, which costs $2,300. Highest costs associated with ALS were seen as the disease progressed into terminal end-stage with costs of mechanical ventilation around $305,985 per year, which is driven mostly by the nursing care costs (16 hours/day) of $23,000 per month or $276,077 per year.

In the United Kingdom, *Munsat et al*. assessed the economic burden of ALS by measuring direct health service costs in relation to the disease progression. All costs were estimated based on interviews of four neurologists specializing in the treatment of ALS. Costs included hospitalization, physician time, inpatient and outpatient laboratory examinations, medical procedures and drug therapy, where prices were determined from the NHS Trust Tariffs for 1996-1997, standard published prices and the Drug Tariff for 1996-1997. Total cost for each ALS health state was measured by applying unit costs to the resources utilized in different stages of the disease. Total annual costs for ALS patients ranged from $2,495 to $1,683 for mild and moderate state and $3,574 to $6,585 for severe and terminal state respectively. The relatively low annual cost for moderate state was due to reductions in hospitalization in this particular state, whereas patients in mild state were likely to be hospitalized for diagnostic related purposes. Nevertheless, the estimated costs presented in this study are significantly lower compared to other studies, especially in terminal state as the cost of mechanical ventilation was not considered for this study. The justification provided by the author states that at the time of the study, expert neurologists did not offer ventilation to patients in their normal clinical practice and thus, it was not discussed in the interviews.

*Athanasakis et al*. investigated the economic burden of ALS in Greece from a societal perspective by taking direct and indirect costs into considerations. Direct costs were obtained from retrospective review of patient records during the period of 2012-2013 that included the costs of medications, physician consultations, diagnostic tests, hospitalizations, rehabilitation care and medical equipment. Indirect costs were obtained from patient

interviews that collected lost productivity from work absenteeism and value of informal care by caregivers. However, the author notes that values of indirect costs were estimated through national minimum wage and thus, the estimated costs do not reflect full accuracy. Total annual costs per patient was $10,311 in which direct costs accounted for 57.8% or $5,958 and indirect costs accounted for the remaining 42.2% or $4,353. While the estimated figure is relatively lower compared to results from other countries, the author notes that lower cost per patient is largely due to lower prices for medications, lower tariffs for healthcare and low wage levels.

*Gladman, Dharamshi, and Zinman* quantified the economic burden of ALS patients and their families by exploring both direct and indirect costs in Canada. Both of the cost components were derived from structured interviews with 50 consecutive ALS patients and their family members. Direct costs consisted of out-of-pocket and government/NPO supported expenses and included costs for home renovation, mobility aids, medical costs, private physical therapy, occupational therapy, and personal social worker services. Indirect costs consisted of income lost due to job loss, permanent disability, early retirement, and any unpaid work absence of patient or their family members. Results have shown that average annual direct cost per patient was $25,285.30 of which $15,305.51 was paid out-of-pocket. The average annual indirect cost per patient and their family members were $44,430.10. The author notes, however, that the study is not generalizable across all ALS patients across Canada as the population that has been captured in this study is derived only from Ontario.

Comparison of economic burden across the studies indicates that costs ranges vary significantly across different countries. This is likely due to units included in direct costs, indirect costs, and nonmedical costs. Moreover, the differences in normal clinical practices across different countries, states, and provinces may have affected the units included in direct costs. In addition, the prices of health services provided across different healthcare systems

would attribute to the difference in the cost range. Nevertheless, all studies mentioned in this section indicate that costs associated with ALS increases as the disease approaches terminal state. Hence, the economic burden of ALS is heavily dependent upon the severity of the disease.

**Cost Effectiveness**

Cost-effectiveness analysis is a method of economic evaluation, which compares both cost and health benefits of different interventions. Cost-effectiveness analysis is a useful tool to guide the decision-making process for allocating resources with a limited budget.

The basic calculation of CEA involves dividing the difference in costs of intervention by the difference in health gain measured in natural units. Cost-effectiveness is often expressed as an incremental cost-effectiveness ratio (ICER) according to the formula:

$$ICER = \frac{(C_T - C_C)}{(E_T - E_C)} = \frac{\Delta C}{\Delta E}$$

Where $C_T$ is the mean costs associated with the new intervention and $C_C$ is the mean costs associated with the comparison intervention. Likewise, $E_T$ and $E_C$ are the mean effectiveness associated with new and comparison intervention respectively. If $\Delta C$ is negative and $\Delta E$ is positive, the new intervention is said to be "dominant" as the new intervention is clearly cost-effective as it is associated with less costs and more clinically effective. Similarly, if $\Delta C$ is positive and $\Delta E$ is negative, the new intervention is not cost-effective or "dominated" as it is both more costly and less clinically effective. When ICER is calculated, it is compared with a threshold value, also known as willingness to pay threshold. The thresholds are higher in developed countries than developing countries. Should the ICER for the new intervention fall

below the threshold value, the new intervention is recommended to be implemented over the existing comparator.

Costs associated with CEA are measured in financial monetary values. On the other hand, health benefits can be measured in various units, such as life years gained (LYG), quality-adjusted life years (QALY), or disability-adjusted life years (DALY) (Robinson, 1993).

A literature review was conducted for cost-effectiveness analysis of riluzole by searching PubMed and Scopus. Articles related to the costs and clinical effectiveness of riluzole for ALS was searched. The full search strategy used for this review can be found in *Appendix C*. Only peer reviewed journals were included in this review and thus, other sources including but not limited to conference abstracts, reports, errata, manufacturer's reports, letters, editorials, and book chapters were excluded. Furthermore, study types other than economic evaluations, or articles written in languages other than English were excluded.

To date, only a handful of economic evaluations were ever conducted to assess the cost effectiveness of riluzole for ALS. All studies included in this review were conducted in Europe using health services perspective. Moreover, all studies used 18 months duration of base data (tracheostomy-free survival) to estimate survival rate. All cost-effectiveness studies in this literature review have been based on results from the two major double-blind placebo-controlled trials (Bensimon et al., 1994; Lacomblez et al., 1996). Variety of methods for estimating survival has been used across the four studies, which include Eyeball, Gompertz, Weibull and Markov models.

The findings across the four studies included in the literature review showed mixed evaluations of riluzole regarding its cost-effectiveness. All studies universally reported a positive survival gain associated with the use of riluzole (0.041 – 6.3 months). Two studies established that riluzole is a cost-effective treatment with ICER per LYG of $18,027 and

$28,451 (Ginsberg & Lev, 1997; Tavakoli et al., 2001). However, the remaining two studies reported riluzole as not cost-effective with ICER per LYG of $73,416 and $90,514 (Gray, 1998; Messori et al., 1999). The full summary of the studies in this literature review are shown in *Table 2*.

Common limitations across all studies were the uncertainties that remained for the economic and survival analysis due to the lack of long term clinical data and utility measurements. Moreover, none of the studies has incorporated home care services or other community services in either the survival or cost component, which are significantly associated with greater extension of survival, quality of life and economic burden for the management of ALS.

Previous research suggests that the proportions of ALS patients in home care, nursing homes, and complex continuing care in Ontario are 69.5%, 11.8%, and 18.7%, respectively (Kehyayan et al., 2014). Due to the progressive nature of the disease, the survival estimates and costs associated with ALS in different care facilities vary widely and thus, it is important that cost-effectiveness studies are conducted using stage-specific estimates accounting for different care settings in order to answer the many uncertainties that exist in the previously published studies and better understand the benefits associated with the use of riluzole.

**Table 2: Summary of review of literature on cost-effectiveness of riluzole**

| Author(s) | Year | Country | Perspective | Duration of base data (tracheostomy-free survival) | | Method for estimating survival | Discount Rate (%) | | Key assumptions | ICER (US $ per LYG) | ICER - Inflation Adjusted [September, 2016] (US $) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Drug | Placebo | | Survival | Costs | | | |
| Ginsberg & Lev | 1997 | Israel | Health Services Society | 18 | 18 | Eyeball | 0 | 5 | 1. Cost benefit included increased productivity (employment) time.<br>2. Cost included monitoring and costs incurred from increased longevity (adverse events, extra outpatient visits, non-riluzole medication use and other costs | 12,013 | 18,027 |
| Gray | 1998 | UK | Health Services | 18 | 18 | N/A | 0 | 0 | 1. Treatment cost included post-tracheostomy costs on monthly basis<br>2. No extrapolations on survival data after 18 months | 50mg - 50,011<br>100mg - 49,200 | 50mg - 74,627<br>100mg - 73,416 |
| Messori et al | 1999 | Italy | Health Services | 18 | 18 | Gompertz | 3 | 3 | 1. Incremental costs other than medication costs and those of drug-related clinical and biochemical moitoring were assumed to be 0. | 62,609 | 90,514 |
| Tavakoli et al | 2001 | UK | Health Services | 18 | 18 | Markov | 0 | 6 | 1. Costs focused on direct costs, and those associated with community care were ignored due to lack of data. | 20,908 | 28,451 |

## Chapter 3: Study Rationale

As pointed out in the literature review section of this thesis, variations in direct costs across different health care systems and survival analysis have presented limitations in producing accurate estimates of cost-effectiveness. Hence, the purpose of this study was to improve on the existing cost-effectiveness analyses by conducting survival analysis from observational data that contains a larger sample size than the conventional RCTs that have been previously used by other studies and estimating accurate costs per QALY gained based on information regarding delays in care transition.

Traditionally, CEA has heavily relied upon RCTs to evaluate the clinical efficacy of drugs. However, in rare conditions such as ALS where the sample size is limited and conducting trials for long period of time may be unfeasible, observational studies may be more useful for assessing the long term effects associated with riluzole. Survival gains from previous research have been estimated from truncated databases with a high degree of uncertainty and thus, observational data was required to fill this gap by providing more accurate stage-specific survival gains.

The main advantage for this study was the use of the OACCAC-HC data, which include person-level clinical assessments along with discharge information for each patient to accurately measure the delay in care transition associated with the use of riluzole. Moreover, cost estimation from the Canadian Institute for Health Information further expanded on direct cost data beyond the existing scope of previous literatures, which improved the understanding of direct cost of medical care associated with ALS in home care.

### 3.1 Research Questions:

1. What are the factors influencing prescription of riluzole for ALS patients?
2. Is riluzole a cost-effective intervention for ALS?

## Chapter 4: Factors influencing prescription of Riluzole for ALS patients in Ontario Home Care

### 4.1 Introduction

Despite the fact that riluzole is the only medication available, drug utilization patterns across patients living with ALS are unclear. There have been no previous studies conducted to identify the factors associated with the prescription of riluzole.

Thus, the objective of this component of the study was to identify and explore the factors influencing the prescription of riluzole for people living with ALS. As there are no clear systematic guidelines determining the prescription candidacy for ALS patients, the present study offers a unique opportunity to investigate the key determinants affecting prescription decisions, which will contribute to the understanding of prescribing patterns of riluzole in Ontario

### 4.2 Methods

#### Design, Sample and Setting

This study was conducted as part of a retrospective cohort study evaluating the cost-effectiveness of Riluzole for ALS in Ontario Home Care using the Ontario Association of Community Care Access Centres – Home Care (OACCAC-HC) data. The OACCAC-HC database houses interRAI's RAI-HC assessments of long stay home care clients within each

of the Ontario Local Health Integration Networks (LHINs). RAI-HC is a standardized comprehensive assessment instrument, which captures information regarding patients' sociodemographic characteristics, mental health status, clinical status, psychosocial status, physical functions, medication use, and receipt of specific services. Since 2002, the RAI-HC assessment has been mandated for all long-stay home care clients with assessment data captured in OACCAC database. The RAI-HC assessments are conducted approximately twice per year.

Embedded within the RAI-HC are scales that provide validated summary measures of individual functioning in specified clinical areas. In this study, six validated scales that summarize functional status in cognition, ADLs, health instability, pain, and mood were examined. The corresponding scales are Cognitive Performance Scale, Activities of Daily Living Self-Performance Hierarchy Scale, Instrumental Activities of Daily Living Involvement Scale, Changes in Health, End-Stage Disease and Signs and Symptoms Scale, Pain Scale, and Depression Rating Scale.

Cognitive Performance Scale (CPS) is a combined measurement of memory impairments, level of consciousness, decision-making skills, and the ability to be understood by others (Morris et al., 1994). The scores range from 0 (intact) to 6 (very severe impairment). Previous studies have reported that CPS is highly correlated to the Mini-Mental State Exam (MMSE), which is a widely used test for cognition status that has been found to be both valid and reliable (Morris et al., 1994).

Activities of Daily Living (ADL) Self-Performance Hierarchy Scale measure one's physical functioning (e.g. dressing, eating, bathing, locomotion, etc.) using selected ADL items that represent stages of the disablement process. The scores range from 0 (independent) to 6 (total dependence), with the additional option where the activity did not occur (8), which is also coded as total dependence. While the ADL Self-Performance Hierarchy Scale was

originally developed for use in the nursing homes, the instrument was proven valid and reliable in home care setting as well (Landi et al., 2000).

The Instrumental Activities of Daily Living (IADL) Involvement Scale is similar to ADL Hierarchy Scale as the instrument also measures one's self-maintenance abilities. However, instead of measuring one's physical functions, the Involvement Scale assesses functioning in routine activities around the home or in the community. The scale is composed of seven items: meal preparation, ordinary housework, managing finances, managing medications, phone use, shopping and transportation. These items are then summed to produce a score that ranges from 0 to 48 with higher scores indicating greater impairments.

The Pain Scale was developed using the Visual Analogue Scale (VAS) as the external standard due to its sensitivity of assessing multiple levels of pain (Fries, Simon, Morris, Flodstrom, & Bookstein, 2001). The scale assesses two items, which are pain frequency and pain intensity. In total, there are four levels, which are no pain (0), less than daily pain (1), daily pain but not severe (2), and daily severe pain (3).

The Depression Rating Scale (DRS) is composed of seven RAI-HC mood items, which are used for clinical assessments to screen for depression. These items are summed together to produce a score which ranges between 0 (no mood symptoms) to 14 (all mood symptoms present). Scores of 3 or greater indicates major or minor depressive disorders. The scale was validated against the Hamilton Depression Rating Scale and the Cornell Scale for Depression, which are the current standard scales used for psychiatric research and dementia respectively (Burrows et al., 2000)

The Changes in Health, End-Stage Disease and Signs and Symptoms (CHESS) Scale was developed to detect health instability and identify individuals at risk for serious decline in functions. The scale assesses nine items which include worsening of decision-making, decline in ADL, vomiting, edema, shortness of breath, end-stage disease, weight loss,

dehydration, and leaving food uneaten. These items are summed to produce a 6-point scale, which ranges from 0 (not at all unstable) to 5 (highly unstable). The scale has been validated to be highly predictive of adverse outcomes such as mortality, hospitalization, pain, caregiver stress, and poor self-rated health (Hirdes, Frijters, & Teare, 2003).

The University of Waterloo retains de-identified copies of OACCAC database as part of a license agreement between interRAI and CIHI. Previous studies and reviews have found RAI instruments to be valid and reliable measures of patient characteristics. (Hirdes, Poss, Mitchell, Korngut & Heckman, 2014; Hirdes et al., 2008; Kim et al., 2015)

The population that has been examined in this study is Ontario long stay home care clients (received service for 60 days or longer) diagnosed with ALS in the province of Ontario. Individuals receiving acute or palliative care do not receive RAI-HC assessments and rather, receive RAI-PC assessment and thus, these individuals are not included in this dataset. RAI-HC assessments for home care clients were collected between January 2002 and March 2015. However, from close consultation with a RAI data specialist, ALS patients with RAI-HC assessment data from April 1$^{st}$, 2005 to March 31$^{st}$, 2013 were included in this study to compensate for the errors during the initial implementation period and in correlation to the 2-year follow-up period that was used for this study. Moreover, patients who were diagnosed with ALS, but had no information on medication use of riluzole were excluded from the study. If the client had multiple assessments in that period, only the baseline assessment was used for the analyses in combination with information on the reason for discharge from home care. Approximately 60% of the study population had multiple assessments. Furthermore, patients who had a history of receiving a tracheostomy were not included in the study.

**Variables**

Data for diagnosis, outcome, exposure, and other clinical assessment variables were drawn from the OACCAC-HC database. The dependent variable for this study was the prescription of riluzole at the time of initial RAI-HC assessment. All the variables that have been included in the model were chosen in correlation to the prognostic factors derived from review of relevant literatures. Independent variables that were thought to be the predictors of outcome and included in this study were: age, gender, geographical location, marital status, availability of caregiver at the time of referral, food consumption, difficulty in swallowing, falls frequency, pressure ulcers, stair climbing, stamina, Cognitive Performance Scale, Activities of Daily Living Hierarchy Scale, Instrumental Activities of Daily Living Involvement Scale, Pain Scale, Depression Rating Scale, and Changes in Health, End-Stage Disease, Signs, and Symptoms Scale.

**Statistical Analyses**

All statistical analyses for this study were conducted using Statistical Analysis Software (SAS), Version 9.4, SAS Institute Inc, Cary, North Carolina, USA. To identify predictors of riluzole prescription, univariate logistic regressions were completed to estimate the odds ratio for each potential predictor. Variables that reached statistical significance ($p < 0.05$) in the univariate analysis were included in the multiple logistic regression. Variables included in the multiple logistic regression were: age, gender, marital status, geographical locations, and Cognitive Performance Scale.

**4.3 Ethics Approval**

This project was cleared for ethics by the Office of Research Ethics at the University of Waterloo on 01 December 2016; ORE #: 21894.

### 4.4 Results

**Descriptive Statistics**

From a total of 1,351 patients diagnosed with ALS, 1,277 patients had information on the use of riluzole. Demographics of study participants are summarized in Table 3.

**Table 3: Demographic characteristics of the study population**

| Baseline Characteristics | No-Riluzole (n = 776) (%) | Riluzole (n = 501) (%) |
|---|---|---|
| **Age (years)** | Mean Age: 67±12.2 | Mean Age: 63±11.4 |
| *18– 45* | 36 (5%) | 34 (7%) |
| *46 – 55* | 91 (12%) | 75 (15%) |
| *56 – 65* | 194 (25%) | 159 (32%) |
| *66 – 75* | 244 (31%) | 151 (30%) |
| *>75* | 211 (27%) | 82 (16%) |
| **Gender** | | |
| *Male* | 401 (52%) | 290 (58%) |
| *Female* | 375 (48%) | 211 (42%) |
| **Marital Status (Married)** | | |
| *Not Married* | 267 (34%) | 126 (25%) |
| *Married* | 509 (66%) | 375 (75%) |
| **Availability of Caregiver** | | |
| *Living Alone* | 132 (17%) | 68 (14%) |
| *Living with spouse or others* | 644 (83%) | 433 (86%) |
| **Geographical Location** | | |
| *Central East* | 70 (9%) | 76 (15%) |
| *Central* | 75 (10%) | 89 (17%) |
| *Champlain* | 111 (14%) | 26 (5%) |
| *Central West* | 28 (4%) | 25 (5%) |
| *Erie St. Clair* | 43 (5%) | 18 (4%) |
| *Hamilton Niagara Haldimand Brant* | 87 (11%) | 48 (10%) |
| *Mississauga Halton* | 69 (9%) | 46 (9%) |
| *North East* | 53 (7%) | 22 (4%) |
| *North Simcoe Muskoka* | 26 (3%) | 18 (4%) |
| *North West* | 15 (2%) | 8 (2%) |
| *South East* | 47 (6%) | 18 (4%) |
| *South West* | 79 (9%) | 37 (7%) |
| *Toronto Central* | 44 (6%) | 46 (9%) |
| *Waterloo Wellington* | 38 (5%) | 24 (5%) |

Overall, study participants were more likely to be males than females, with majority being over 55 years of age. More than half of the study populations were not taking riluzole

at the time of the initial assessment. The mean age was 67 years old in the non-riluzole group and 63 years old in the riluzole group. The proportions of subjects who were married were higher in the riluzole group than the non-riluzole group. Clinical characteristics of both groups are summarized in Table 4. Both groups appeared to have very similar clinical status at the time of the initial assessment.

**Table 4: Summary of Clinical Characteristics**

| **Baseline Characteristics** | **No-Riluzole (n = 776) (%)** | **Riluzole (n = 501) (%)** |
|---|---|---|
| **Weight Loss** | | |
| *No* | 580 (75%) | 390 (78%) |
| *Yes* | 196 (25%) | 111 (22%) |
| **Food Consumption: Ate one or fewer meals in at least 2 of the last 3 days** | | |
| *No* | 734 (95%) | 468 (93%) |
| *Yes* | 42 (5%) | 33 (7%) |
| **Difficulty Swallowing** | | |
| *No* | 398 (51%) | 256 (51%) |
| *Yes* | 378 (49%) | 245 (49%) |
| **Falls** | | |
| *No* | 351 (45%) | 227 (45%) |
| *Yes* | 425 (55%) | 274 (55%) |
| **Pressure Ulcers** | | |
| No | 748 (96%) | 484 (97%) |
| Yes | 28 (4%) | 17 (3%) |
| **Stamina – Hours of physical activities in the last 3 days** | | |
| *Less than two hours* | 313 (40%) | 184 (37%) |
| *Two or more hours* | 463 (60%) | 317 (63%) |
| **Stair Climbing** | | |
| *Without Help* | 283 (36%) | 190 (38%) |
| *With Help / No Climb* | 493 (64%) | 311 (62%) |
| ***CPS Scale*** | **Mean Score:** 0.61 ± 0.98 | **Mean Score:** 0.48 (±0.92) |
| *0 (Intact) – (Reference)* | 486 (63%) | 338 (67%) |
| *1-2 (Borderline intact – Mild impairment)* | 244 (31%) | 151 (30%) |
| *3-4 (moderate – Moderate severe impairment)* | 39 (5%) | 5 (1%) |
| *5-6 (Severe – Very severe impairment* | 7 (1%) | 7 (2%) |

| **ADL Hierarchy Scale** | **Mean Score:** 1.73 ± 1.83 | **Mean Score:** 1.69 ± 1.86 |
|---|---|---|
| *0 (Independent) – (Reference)* | 310 (40%) | 216 (43%) |
| *1-2 (Supervision required – limited impairment)* | 233 (30%) | 138 (28%) |
| *3+ (Extensive assistance required – total dependence)* | 233 (30%) | 147 (29%) |
| **IADL Involvement Scale** | **Mean Score:** 11.96 ± 5.34 | **Mean Score** 12.05 ± 5.64 |
| **Pain Scale** | **Mean Score**: 1.13 ± 1.10 | **Mean Score:** 1.15 ± 1.15 |
| *0 (No pain) – (Reference)* | 337 (44%) | 221 (44%) |
| *1-2 (Less than daily pain – Daily pain not severe)* | 374 (48%) | 226 (45%) |
| *3+ (Daily severe pain)* | 65 (8%) | 54 (11%) |
| **Depression Rating Scale** | **Mean Score:** 1.62 ± 2.20 | **Mean Score:** 1.58 ± 2.25 |
| *0 -2 (No depression)* | 577 (74%) | 380 (76%) |
| *3+ (Minor or Major Depression)* | 199 (26%) | 121 (24%) |
| **CHESS Scale** | **Mean Score:** 1.65 ± 1.01 | **Mean Score:** 1.62 ± 1.02 |
| *0 (Not at all unstable) – (Reference)* | 91 (12%) | 58 (12%) |
| *1-2 (Little – Some instability)* | 518 (67%) | 341 (68%) |
| *3+ (Moderately – Highly unstable)* | 167 (21%) | 102 (20%) |

**Univariate and Multiple Logistic Regression**

Predictors of receipt of riluzole are presented in Table 5. In the univariate analysis, older age, male gender, moderate – moderate severe impairment in cognitive functions and geographical locations across LHINs (Champlain, Erie St. Clair, Hamilton Niagara Haldimand Brant, North East, South East, and South West) reduced the likelihood of riluzole prescription. Being married was the only predictor associated with increased likelihood of riluzole prescription.

**Table 5: Univariate Logistic Regression Analysis**

| Variables | OR (95% CI) | P-value |
|---|---|---|
| **Age** | 0.977 (0.968 – 0.987) | <0.0001 |
| **Gender** | 0.778 (0.620 – 0.976) | 0.029 |
| **Weight Loss** | 0.842 (0.646 – 1.099) | 0.206 |
| **Food Consumption: Ate one or fewer meals in at least 2 of the last 3 days** | 1.232 (0.770 – 1.973) | 0.384 |
| **Difficulty Swallowing** | 1.008 (0.805 – 1.262) | 0.947 |
| **Falls Frequency** | 0.997 (0.795 – 1.249) | 0.978 |
| **Pressure Ulcers** | 0.939 (0.508 – 1.733) | 0.840 |
| **Stamina – Hours of physical activities in the last 3 days** | 1.165 (0.924 – 1.468) | 0.197 |
| **Stair Climbing** | 0.940 (0.745 – 1.185) | 0.599 |
| **Marital Status** | 1.561 (1.215 – 2.005) | 0.0005 |
| **Availability of Caregiver** | 1.305 (0.951 – 1.792) | 0.099 |
| **Geographical Location** | | |
| *Central East* | 1.039 (0.614 – 1.757) | 0.888 |
| *Central* | 1.135 (0.678 – 1.900) | 0.630 |
| *Champlain* | 0.224 (0.124 – 0.406) | <.0001 |
| *Central West* | 0.854 (0.433 – 1.685) | 0.649 |
| *Erie St. Clair* | 0.400 (0.201 – 0.797) | 0.009 |
| *Hamilton Niagara Haldimand Brant* | 0.528 (0.307 – 0.908) | 0.021 |
| *Mississauga Halton* | 0.638 (0.365 – 1.113) | 0.113 |
| *North East* | 0.397 (0.208 – 0.758) | 0.005 |
| *North Simcoe Muskoka* | 0.662 (0.319 – 1.373) | 0.268 |
| *North West* | 0.510 (0.197 – 1.322) | 0.166 |
| *South East* | 0.366 (0.185 – 0.725) | 0.004 |
| *South West* | 0.506 (0.285 – 0.898) | 0.020 |
| *Toronto Central (Reference)* | | |
| *Waterloo Wellington* | 0.604 (0.313 – 1.166) | 0.133 |
| **CPS Scale** | | |
| *0 (Intact) – (Reference)* | | |
| *1-2 (Borderline intact – Mild impairment)* | 0.890 (0.696 – 1.138) | 0.352 |
| *3-4 (moderate – Moderate severe impairment)* | 0.184 (0.072 – 0.473) | 0.0004 |
| *5-6 (Severe – Very severe impairment* | 1.438 (0.500 – 4.137) | 0.501 |
| **ADL Hierarchy Scale** | | |
| *0 (Independent) – (Reference)* | | |
| *1-2 (Supervision required – limited impairment)* | 0.850 (0.647 – 1.117) | 0.243 |
| *3+ (Extensive assistance required – total dependence)* | 0.905 (0.691 – 1.186) | 0.471 |
| **IADL Involvement Scale** | 1.003 (0.983 – 1.024) | 0.778 |
| **Pain Scale** | | |
| *0 (No pain) – (Reference)* | | |
| *1-2 (Less than daily pain – Daily pain not severe)* | 0.921 (0.727 – 1.168) | 0.498 |
| *3+ (Daily severe pain)* | 1.267 (0.850 – 1.888) | 0.245 |

| | | |
|---|---|---|
| **Depression Rating Scale** | 0.923 (0.712 – 1.198) | 0.548 |
| **CHESS Scale** | | |
| *0 (Not at all unstable) – (Reference)* | | |
| *1-2 (Little – Some instability)* | 1.033 (0.723 – 1.475) | 0.859 |
| *3+ (Moderately – Highly unstable)* | 0.959 (0.635 – 1.446) | 0.840 |

**Table 6: Multiple Logistic Regression Analysis**

| Variables | OR (95% CI) | P-value |
|---|---|---|
| **Age** | 0.975 (0.964 – 0.985) | <.0001 |
| **Gender** | 0.887 (0.691 – 1.140) | 0.349 |
| **Marital Status** | 1.637 (1.247 – 2.148) | 0.0004 |
| **Geographical Location** | | |
| *Central East* | 0.878 (0.506 – 1.525) | 0.645 |
| *Central* | 0.940 (0.547 – 1.615) | 0.822 |
| *Champlain* | 0.189 (0.102 – 0.351) | <.0001 |
| *Central West* | 0.838 (0.411 – 1.708) | 0.626 |
| *Erie St. Clair* | 0.314 (0.154 – 0.644) | 0.002 |
| *Hamilton Niagara Haldimand Brant* | 0.412 (0.233 – 0.730) | 0.002 |
| *Mississauga Halton* | 0.536 (0.299 – 0.962) | 0.037 |
| *North East* | 0.300 (0.152 – 0.591) | 0.0005 |
| *North Simcoe Muskoka* | 0.580 (0.272 – 1.236) | 0.158 |
| *North West* | 0.489 (0.182 – 1.314) | 0.156 |
| *South East* | 0.311 (0.153 – 0.631) | 0.001 |
| *South West* | 0.417 (0.228 – 0.761) | 0.004 |
| *Toronto Central (Reference)* | | |
| *Waterloo Wellington* | 0.504 (0.253 – 1.003) | 0.051 |
| **CPS Scale** | | |
| *0 (Intact) – (Reference)* | | |
| *1-2 (Borderline intact – Mild impairment)* | 0.974 (0.749 – 1.265) | 0.842 |
| *3-4 (moderate – Moderate severe impairment)* | 0.201 (0.076 – 0.530) | 0.001 |
| *5-6 (Severe – Very severe impairment* | 1.328 (0.437 – 4.034) | 0.617 |

In the multiple logistic regression analysis (shown in Table 6), four of five variables reached statistical significance. Older age, moderate – moderate severe impairment in cognitive functions and geographical locations across LHINs (Champlain, Erie St. Clair, Hamilton Niagara Haldimand Brant, Mississauga Halton, North East, South East, and South West) decreased the likelihood of riluzole prescription. Being married increased the likelihood of riluzole prescription. Gender was not considered as statistically significant in the multiple logistic regression analysis.

**Figure 1: Odds ratio of riluzole prescription across each LHINs vs. Toronto Central Network**

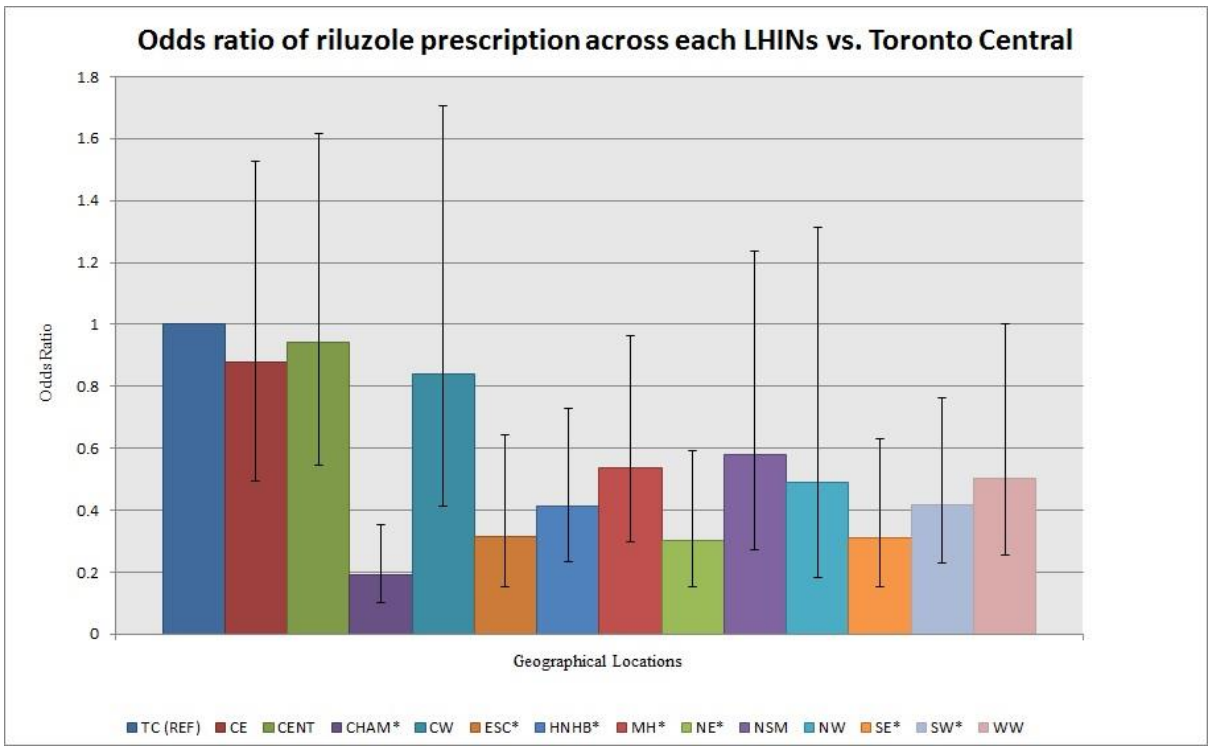
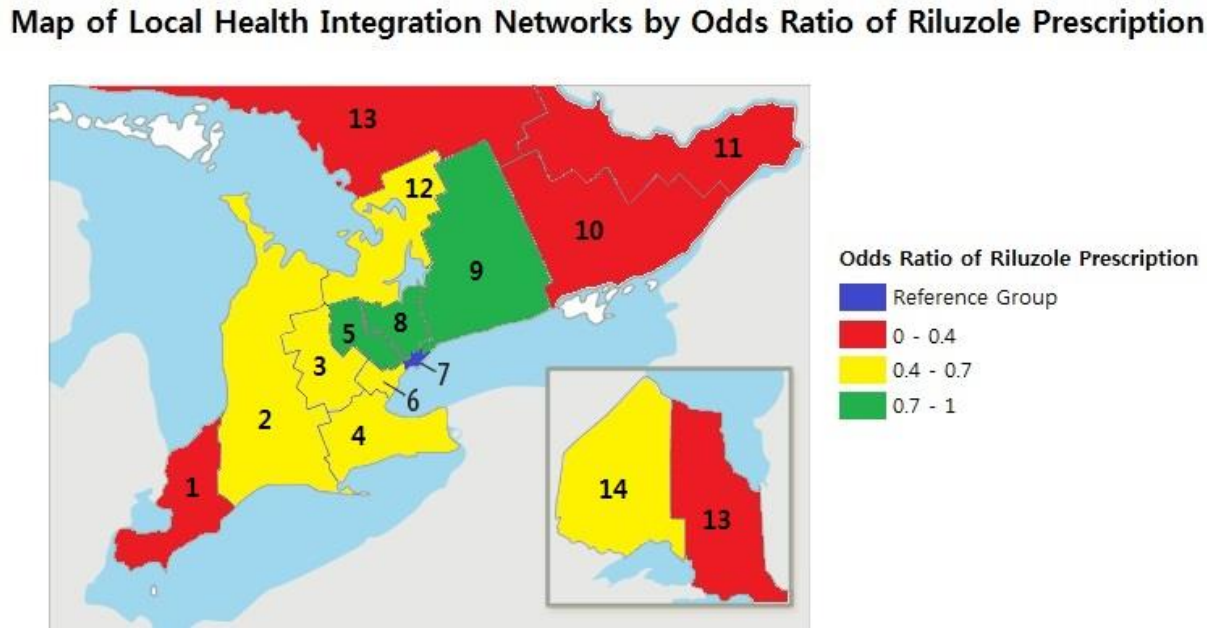



**Figure 2: Map of LHINs by Odds Ratio of Riluzole Prescription**



### 4.5 Discussion

To our knowledge, this study is the first of its kind examining the predictors affecting the likelihood of receiving riluzole for the treatment of ALS. The results of this study show that the prevalence of riluzole use among ALS patients in Ontario home care setting was 39.2%, which is relatively low considering the fact that riluzole is the only drug approved for the treatment of ALS.

According to the study results, younger patients were more likely to be prescribed to riluzole. Moreover, patients who were married were more likely to receive riluzole than patients who lived alone; this is despite the fact that patients who are older and living alone have worse prognosis than patients who are young and married, and thus may have more to gain from the medication (Chio et al., 2008). One explanation may be that older patients are more prone to drug adverse events and living with other comorbidities, which may discourage physicians from prescribing riluzole.

The results also showed that the likelihood of riluzole prescription is heavily dependent upon one's geographical residency. Toronto Central was chosen as the reference group in this study as most academic institutions are concentrated in this area. Patients living further away from Toronto Central were less likely to be prescribed to riluzole. Nor do the results reflect the absence of ALS clinics, which are located in Hamilton (HNHB), Kingston (SE), London (SW), Ottawa (CHAM), Thunder Bay (NW), and Toronto (TC). The reason for this disparity cannot be explained with the current data. However, the results indicate that potential regional health inequities might be present for the treatment of ALS. As riluzole is proven to have modest benefits, it can be hypothesized that if a patient who is treated in an institution with more use of riluzole, then the institution is more likely to be using other best practices to manage ALS. However, using riluzole as a marker for care quality should be further investigated.

The present study had several limitations. As the data only captured information drawn from the initial admission assessments, the results do not reflect the use of riluzole throughout the entire home care stay. Secondly, as 1,277 out of 1,351 patients had information on the use of riluzole, 74 observations or 9.5% of the total population has been excluded from the study. Thus, the present study may have underestimated (or overestimated) the prevalence use of riluzole. Lastly, it is important to note that while all variables were carefully chosen in correlation to the prognostic factors identified in the literature, the study may not have captured all relevant variables that are related to the outcome. Moreover, the study did not account for the unmeasured covariates (e.g. income level, caregiver stress), which may play a critical role for the prescription of riluzole.

In conclusion, this study identified many important predictors associated with the receipt of riluzole, and thus target physicians and policymakers to promote the proper use of the drug. Patients' characteristics such as older age, moderate cognitive score, not being married and geographical locations across LHINs decreased the likelihood of receiving riluzole. Further research on physician behaviors and routine clinical practices across LHINs are required to better understand the factors associated with the prescription of riluzole. In addition, further research is necessary on whether or not the use of riluzole is a marker of other areas of care quality for the treatment of ALS.

## Chapter 5: Cost-effectiveness of Riluzole

### 5.1 Methods

#### Basic Design

A retrospective cohort study of OACCAC-HC assessment data was carried out to perform the survival analysis in order to estimate the delay in care transitions in HC. Assessment data were collected at the time of admission and patients receive additional assessments approximately every six months. For cost analysis, cost information was derived from previously published journals and Canadian Institute for Health Information Patient Cost Estimator (CIHI-PCE). Although secondary data analyses pose several limitations, analyses through the availability of high quality clinical assessments, along with the long-term observational data establishes a unique approach that has never been performed in cost-effectiveness analysis for riluzole.

#### Study Sample and Setting

As the present study involved secondary data analyses, no subject recruitment was required. All subjects were drawn from the OACCAC-HC database, with specific focus on patients with diagnosis of ALS. The population that was examined in this study was Canadian long stay home care clients (those expected to be on service for 60 days or longer) diagnosed with ALS in the province of Ontario. Individuals receiving acute or palliative care do not receive RAI-HC assessments and rather, receive RAI-PC assessment and thus, these individuals were not included in this dataset. RAI-HC assessments for home care clients were collected between January 2002 and March 2015. However, from close consultation with a RAI data specialist, home care clients with RAI-HC assessment data from April 1$^{st}$, 2005 to March 31$^{st}$, 2013 were eligible for this study to compensate for the errors during the initial

implementation period and in correlation to the 2-year follow-up period that was used for this study. If the client had multiple assessments in that period, only the baseline assessment was used for the analyses. Approximately 60% of the study population had multiple assessments. Furthermore, patients who had a history of receiving a tracheostomy were not included in the study.

The data for this proposed study was provided by the OACCAC, which manages the RAI-HC database of home care clients within each of the Ontario Local Health Integration Networks (LHINs). RAI-HC is a standardized comprehensive assessment instrument that captures information regarding clients' sociodemographic characteristics, clinical status, mental health status, psychosocial status, physical functions, medication use, and receipt of specific services (Morris, Fries, Morris, 1999). Since 2002, the RAI-HC assessment has been mandated for all long-stay home care clients with assessment data captured in OACCAC database.

Embedded within the RAI-HC are scales that provide validated summary measures of individual functioning in specified clinical areas. In this study, seven validated scales that summarize functional status in cognition, ADLs, health instability, pain, and mood will be examined. The corresponding scales are Cognitive Performance Scale, Activities of Daily Living Self-Performance Hierarchy Scale, Instrumental Activities of Daily Living Scale, Changes in Health, End-stage Disease and Signs and Symptoms Scale, Pain Scale, Depression Rating Scale, and Method for Assigning Priority Levels scale.

Cognitive Performance Scale (CPS) is a combined measurement of memory impairments, level of consciousness, decision-making skills, and the ability to be understood by others (Morris et al., 1994). The scores range from 0 (intact) to 6 (very severe impairment). Previous studies have reported that CPS is highly correlated to the Mini-Mental State Exam (MMSE), which is a widely used test for cognition status that has been found to be both valid

and reliable (Morris et al., 1994).

Activities of Daily Living (ADL) Self-Performance Hierarchy Scale measure one's physical functioning (e.g. dressing, eating, bathing, locomotion, etc.) using selected ADL items that represent stages of the disablement process. The scores range from 0 (independent) to 6 (total dependence), with the additional option where the activity did not occur (8), which is also coded as total dependence. While the ADL Self-Performance Hierarchy Scale was originally developed for use in the nursing homes, the instrument was proven valid and reliable in home care setting as well (Landi et al., 2000).

The Instrumental Activities of Daily Living (IADL) Involvement Scale is similar to ADL Hierarchy Scale as the instrument also measures one's self-maintenance abilities. However, instead of measuring one's physical functions, the Involvement Scale assesses functioning in routine activities around the home or in the community. The scale is composed of seven items: meal preparation, ordinary housework, managing finances, managing medications, phone use, shopping and transportation. These items are then summed to produce a score that ranges from 0 to 48 with higher scores indicating greater impairments.

The Pain Scale was developed using the Visual Analogue Scale (VAS) as the external standard due to its sensitivity of assessing multiple levels of pain (Fries, Simon, Morris, Flodstrom, & Bookstein, 2001). The scale assesses two items, which are pain frequency and pain intensity. In total, there are four levels, which are no pain (0), less than daily pain (1), daily pain but not severe (2), and daily severe pain (3). Once again, the scale was originally developed and highly predictive of pain for nursing home residents; however, the instrument has not yet been validated for home care population (Fries et al., 2001).

The Depression Rating Scale (DRS) is composed of seven RAI-HC mood items, which are used for clinical assessments to screen for depression. These items are summed together to produce a score which ranges between 0 (no mood symptoms) to 14 (all mood

symptoms present). Scores of 3 or greater indicates major or minor depressive disorders. The scale was validated against the Hamilton Depression Rating Scale and the Cornell Scale for Depression, which are the current standard scales used for psychiatric research and dementia respectively.

The Changes in Health, End-Stage Disease and Signs and Symptoms (CHESS) Scale was developed to detect health instability and identify individuals at risk for serious decline in functions. The scale assesses nine items which include worsening of decision-making, decline in ADL, vomiting, edema, shortness of breath, end-stage disease, weight loss, dehydration, and leaving food uneaten. These items are summed to produce a 6-point scale, which ranges from 0 (not at all unstable) to 5 (highly unstable). The scale has been validated to be highly predictive of adverse outcomes such as mortality, hospitalization, pain, caregiver stress, and poor self-rated health (Hirdes, Frijters, & Teare, 2003).

The Methods for Assigning Priority Levels (MAPLe) scale was developed to be a predictor for institutionalization and used as an indicator for allocation of home care resources and prioritization among home care clients (Hirdes, Poss & Curtin-Telegdi, 2008). MAPLe is an internationally validated predictor of nursing home placements, caregiver distress, and ratings that client would be served better in another care setting (Hirdes et al., 2008). The algorithm was derived from the MDC-HC data from Ontario, Canada and validated with samples of home care clients from three other provinces (British Columbia, Manitoba, and Nova Scotia) and five other countries (Iceland, Italy, Japan, Sweden, and United States) (Hirdes et al., 2008). The scale ranges from 1 (Low) to 5 (Very High).

The University of Waterloo retains de-identified copies of OACCAC database as part of a license agreement between InterRAI and CIHI. Previous studies and reviews have found RAI instruments to be valid and reliable measures of patient characteristics (Hirdes, Poss, Mitchell, Korngut & Heckman, 2014; Hirdes et al., 2008; Kim et al., 2015).

**Propensity Score**

Propensity score is the probability of treatment assignment dependent upon patients' observed baseline characteristics (Austin, 2011; Rosenbaum & Rubin, 1984). Propensity score is a balancing score which measures the likelihood that a patient would have been treated using only their covariate scores (Austin, 2011; Rosenbaum & Rubin, 1984). In most cases, randomized clinical trials are the gold standard approach in determining the efficacy of a drug on outcomes. The randomization ensures no selection bias and thus, there are no systematic differences in observed and unobserved covariates between the comparison groups (Austin, 2011). Since the OACCAC-HC is an observational database, adjustments for potential bias due to the confounding variables are required since assignments of riluzole cannot be assumed to be random. Hence, measurement of the propensity score allowed the study to create a quasi-experiment, which reduced the possibility of bias.

**Measurements**

Data for diagnosis, outcome, exposure, and other clinical assessment variables were drawn from the OACCAC-HC database. The diagnosis of interest was ALS, while the main outcome of interest was the time to discharge from home care, which included death, placement into long-term care, and hospitalization. Moreover, exposure of interest was the prescription for riluzole (riluzole vs. no riluzole), while clinical assessment variables were those suspected to be the predictors of outcome.

In order to calculate the propensity score, observed covariates that affect both treatment selection and outcome were first identified (Stuart, 2010). These variables were chosen in correlation to the prognostic factors that were identified earlier in the literature review section. The independent variables that were included in this section mirror much of the variables that were included in Chapter 4 of this thesis. However, as Bryson, Dorsett &

Purdon (2002) pointed out that having too many variables may increase variance in the propensity score calculation, individual items such as food consumption, difficulty in swallowing, falls frequency, pressure ulcers, stair climbing, and stamina were replaced with Methods for Assigning Priority Levels (MAPLe) scale, which is a scale that incorporates the aforementioned variables into its scoring criteria.

The following RAI-HC items were examined for estimating propensity score: clients' sociodemographic status (age, gender, geographical location); psychosocial characteristics (marital status & availability of caregiver); health status (cognitive impairments, functional impairments, health instability, pain, depression, prioritization level); and medication use (riluzole).

## 5.2 Analysis

### Software

All statistical analyses for this study were carried out using Statistical Analysis Software (SAS), Version 9.4 (SAS Institute, Cary, NC, USA).

### Ethics Approval

This project was cleared for ethics by the Office of Research Ethics at the University of Waterloo on 01 December 2016; ORE #: 21894.

### Estimation of Propensity Score

Once the variables had been selected, multivariate logistic regression was used to estimate the propensity scores. The covariates were used in a logistic regression to predict the exposure of interest (riluzole vs. non-riluzole), excluding the outcome, which is the time to discharge from home care. Hence, dependent variable was the treatment group (1 = treatment,

0 = control), while independent variables were the observed baseline covariates. Essentially, all the variables that were included in the model were collapsed into a 'single' variable, which is the probability of being exposed to the treatment: propensity scores.

**Adjustments**

Once the propensity score has been estimated, stratification was used to adjust for the covariates prior to estimating the treatment effect. Stratification consisted of grouping subjects into strata by estimated propensity scores and allowed for direct comparison of treated and control subjects in the same strata. Previous research suggests that creating five strata based on the propensity score removes approximately 90% of bias in all covariates when estimating a linear treatment effect (Rosenbaum & Rubin, 1984). Hence, subjects were stratified into five, approximately equally sized quintiles from the estimated propensity score.

To show that the propensity scores removed any bias due to covariate differences across the two treatment groups, bivariate tests were conducted for each covariate prior to propensity score estimation. T-tests were conducted for continuous variables and chi-square tests were conducted for categorical variables. Then, the GLM procedure was used to calculate the least square means and corresponding p-values for each covariate adjusted for propensity scores, which were used to assess the differences between the treatment groups before and after stratifying subjects by the propensity scores. Moreover, interaction plots for each variable were constructed to assess balance across all propensity score quintiles.

**Survival Analysis**

Kaplan-Meier (K-M) survival curves were constructed separately for treated and untreated groups in each propensity score stratum to assess the time to discharge over 2-year period. To estimate the effect of treatment in the overall population (Average Treatment

Effect), each stratum was weighted by the number of subjects within the stratum, in order to create a pooled analysis of stratum-specific K-M curves to obtain a population-average survival curve. Cox proportional hazards regression model was used to produce hazard ratios by using treatment status and propensity score quintiles as covariates.

**Cost Analysis**

As this study was conducted using the health services perspective (Ministry of Health and Long-Term Care), only direct costs were considered in the cost analysis. Direct costs included in this study were: cost of standard supportive home care services, which consists of nursing visits, shifts nursing hours, personal support hours, physical therapy visits, occupational therapy visits, speech language therapy visits, social work visits, dietician visits and administration of 100 mg of riluzole on daily basis. Moreover, estimated average costs for staying in long-term care and hospital after discharge from home care was used as a cost-offset factor. Costs were adjusted for inflation to 2016 Canadian dollars using the consumer price index for healthcare in Ontario. Moreover, annual discount rate of 3% was applied to both benefits and costs as suggested by the WHO Guideline to Cost-Effectiveness Analysis. Indirect medical costs were not included as they were not relevant to the perspective of this analysis. The cost estimates were derived from information published in multiple sources including CIHI-PCE and relevant literatures.

To evaluate the cost-effectiveness of riluzole therapy compared to standard supportive care therapy, the incremental cost effectiveness ratio (ICER) per life-year gained, that is, the difference in cost between riluzole therapy (including cost-offset factors) and standard care therapy divided by the difference in median survival was calculated as follows:

$$ICER = (Cost_{Riluzole} - Cost_{StandardTherapy}) / (Survival_{Riluzole} - Survival_{StandardTherapy}).$$

In addition to calculating the ICER per life-year gained, incremental cost per quality-adjusted life years (QALY) gained was measured. Health state utility scores that were required to measure the QALYs were derived from information published in the relevant literatures that assessed the utility scores in each stages of ALS.

**Sensitivity Analysis:**

One-way deterministic sensitivity analyses were carried out in a ± 20% range of each base case parameters, which included all costs, health utility scores, and survival differences (time to discharge from home care). In addition, scenario analyses were conducted by constructing best and worst case scenarios, which involved alterations of multiple parameters simultaneously. The best case scenario involved changing parameters in the most optimistic way to produce the most favorable ICER, whereas the worst case scenario involved changing parameters in the most pessimistic way to produce the least favorable ICER.

## 5.3 Results

**Descriptive Statistics**

From a total of 1,351 patients diagnosed with ALS, 1,277 patients had information on the use of riluzole. Demographics of study participants are summarized in *Table 7*.

**Table 7: Demographic characteristics of the study population**

| **Baseline Characteristics** | **No-Riluzole (n = 776) (%)** | **Riluzole (n = 501) (%)** |
|---|---|---|
| **Age (years)** | **Mean Age:** 67±12.2 | **Mean Age:** 63±11.4 |
| *18 – 45* | 36 (5%) | 34 (7%) |
| *46 – 55* | 91 (12%) | 75 (15%) |
| *56 – 65* | 194 (25%) | 159 (32%) |
| *66 – 75* | 244 (31%) | 151 (30%) |
| *>75* | 211 (27%) | 82 (16%) |

| **Gender** | | |
|---|---|---|
| *Male* | 401 (52%) | 290 (58%) |
| *Female* | 375 (48%) | 211 (42%) |
| **Marital Status (Married)** | | |
| *Not Married* | 267 (34%) | 126 (25%) |
| *Married* | 509 (66%) | 375 (75%) |
| **Availability of Caregiver** | | |
| *Living Alone* | 132 (17%) | 68 (14%) |
| *Living with spouse or others* | 644 (83%) | 433 (86%) |
| **Geographical Location** | | |
| *Central East* | 70 (9%) | 76 (15%) |
| *Central* | 75 (10%) | 89 (17%) |
| *Champlain* | 111 (14%) | 26 (5%) |
| *Central West* | 28 (4%) | 25 (5%) |
| *Erie St. Clair* | 43 (5%) | 18 (4%) |
| *Hamilton Niagara Haldimand Brant* | 87 (11%) | 48 (10%) |
| *Mississauga Halton* | 69 (9%) | 46 (9%) |
| *North East* | 53 (7%) | 22 (4%) |
| *North Simcoe Muskoka* | 26 (3%) | 18 (4%) |
| *North West* | 15 (2%) | 8 (2%) |
| *South East* | 47 (6%) | 18 (4%) |
| *South West* | 79 (9%) | 37 (7%) |
| *Toronto Central* | 44 (6%) | 46 (9%) |
| *Waterloo Wellington* | 38 (5%) | 24 (5%) |

Overall, study participants were more likely to be males than females, which is consistent with other studies that reported the incidences of ALS are more common in men. Majority of the study populations were over 55 years of age with the mean age of 67 years old in the non-riluzole group and 63 years old in the riluzole group. The proportions of subjects who were married were higher in the riluzole group than the non-riluzole group.

**Table 8: Summary of clinical characteristics**

| **Baseline Characteristics** | **No-Riluzole (n = 776) (%)** | **Riluzole (n = 501) (%)** |
|---|---|---|
| ***CPS Scale*** | **Mean Score:** 0.61 ± 0.98 | **Mean Score:** 0.48 (±0.92) |
| *0 (Intact) – (Reference)* | 486 (63%) | 338 (67%) |
| *1-2 (Borderline intact – Mild impairment)* | 244 (31%) | 151 (30%) |

| | | |
|---|---|---|
| *3-4 (moderate – Moderate severe impairment)* | 39 (5%) | 5 (1%) |
| *5-6 (Severe – Very severe impairment* | 7 (1%) | 7 (2%) |
| **ADL Hierarchy Scale** | **Mean Score:** 1.73 ± 1.83 | **Mean Score:** 1.69 ± 1.86 |
| *0 (Independent) – (Reference)* | 310 (40%) | 216 (43%) |
| *1-2 (Supervision required – limited impairment)* | 233 (30%) | 138 (28%) |
| *3+ (Extensive assistance required – total dependence)* | 233 (30%) | 147 (29%) |
| **IADL Involvement Scale** | **Mean Score:** 11.96 ± 5.34 | **Mean Score** 12.05 ± 5.64 |
| **Pain Scale** | **Mean Score**: 1.13 ± 1.10 | **Mean Score:** 1.15 ± 1.15 |
| *0 (No pain) – (Reference)* | 337 (44%) | 221 (44%) |
| *1-2 (Less than daily pain – Daily pain not severe)* | 374 (48%) | 226 (45%) |
| *3+ (Daily severe pain)* | 65 (8%) | 54 (11%) |
| **Depression Rating Scale** | **Mean Score:** 1.62 ± 2.20 | **Mean Score:** 1.58 ± 2.25 |
| *0 -2 (No depression)* | 577 (74%) | 380 (76%) |
| *3+ (Minor or Major Depression)* | 199 (26%) | 121 (24%) |
| **CHESS Scale** | **Mean Score:** 1.65 ± 1.01 | **Mean Score:** 1.62 ± 1.02 |
| *0 (Not at all unstable) – (Reference)* | 91 (12%) | 58 (12%) |
| *1-2 (Little – Some instability)* | 518 (67%) | 341 (68%) |
| *3+ (Moderately – Highly unstable)* | 167 (21%) | 102 (20%) |
| **MAPLe Scale** | **Mean Score:** 3.03 ± 1.16 | **Mean Score:** 2.92 ± 1.18 |
| *1 (Low)* | 149 (19%) | 111 (22%) |
| *2 – 3 (Mild – moderate)* | 304 (39%) | 194 (39%) |
| *4 – 5 (High – very high)* | 323 (42%) | 196 (39%) |

*Table 8* depicts the clinical characteristics of the study population. Patients in the riluzole group were less likely to have moderate – moderately severe impairment in cognitive functions than the non-riluzole group. Otherwise, the overall clinical statuses between the two groups were very similar to each other.

**Table 9: Discharge Reasons from Home Care**

| | Discharge Reasons | | | |
|---|---|---|---|---|
| | **Death** | **Long-Term Care** | **Hospitalization** | **Others** |
| **No Riluzole** | N = 348 (44.85%) | N = 59 (7.60%) | N = 121 (15.59%) | N = 248 (31.96%) |
| **Riluzole** | N = 254 (50.70%) | N = 33 (6.60%) | N = 61 (12.18%) | N = 153 (30.52%) |

Table 9 depicts the proportion of discharge reasons across the two treatment groups. More patients who were taking riluzole were discharged from home care due to death. Approximately same amount of patients were placed into long-term care, while more patients who were not taking riluzole were hospitalized compared to patients who were taking riluzole. Reasons for discharge from home care other than death, placement into long-term care, or hospitalization include: completion of service plan, transfer to other CCAC, client preference, opted for other community services, and vacation over 30 days.

**Propensity Score**

Propensity scores for each individual were calculated by fitting a logistic regression model to estimate all covariates shown in demographic profiles and clinical characteristics depicted in Table 7 and Table 8 on the probability of receiving riluzole.

**Figure 3: Histogram - Distribution of Propensity Score by Treatment Group**

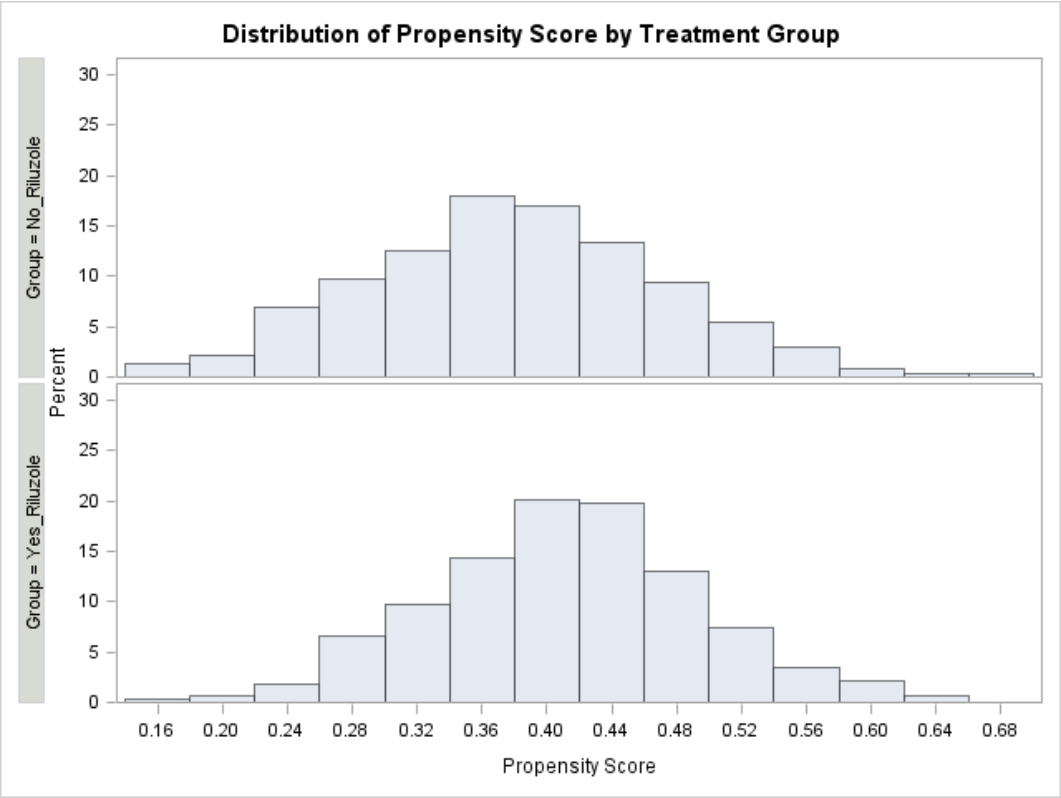
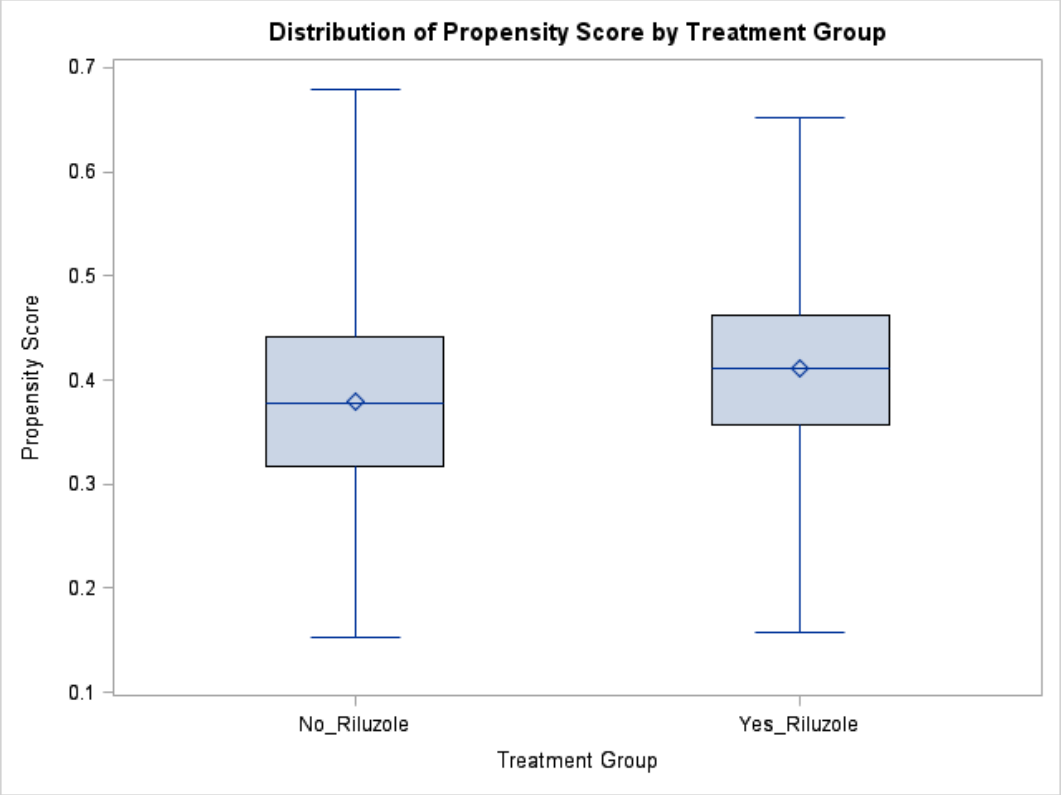



**Figure 4: Boxplot – Distribution of Propensity Score by Treatment Group**



Histogram and boxplot shown in *Figure 3* and *Figure 4* depicts the distribution of propensity score by treatment group, which shows that propensity score in the riluzole group was higher than the non-riluzole group, with mean score of 0.41 and 0.38 respectively. The propensity scores vary from 0.16 to 0.68 and there is a good degree of overlap across the two treatment groups.

**Propensity Score Adjustments**

Propensity score stratification was used as an adjustment method for this study. Based on each patient's respective propensity score, all individuals were ranked and stratified into five quintiles in an increasing order. Quintile 1 represents those with the lowest propensity scores, while quintile 5 represents those with the highest propensity scores. As shown in *figure 5*, the propensity scores between treatment groups are very similar to one another in each of the quintiles.

Results from bivariate tests and GLM procedure are shown in *Table 10*. Mean value for each variable along with p-values for both treatment groups prior to propensity score estimation and least square means and p-values adjusted for propensity scores are reported in the table. Results indicate that age (p=<.0001), gender (p=0.029), geographical locations (p=<0.0001), marital status (p=0.0005), and CPS (p=0.0008) had statistically significant differences across the two treatment groups. However, adjusted p-values for all the aforementioned variables are >0.05, indicating that differences among the two treatment groups are no longer statistically significant. Moreover, mean value for each covariate was widely different across the two treatment groups prior to propensity score estimation. However, least mean squares adjusted for propensity scores indicate that mean value for each covariate are very similar across the two treatment groups.

In addition, interaction plots were constructed to assess balance across all five quintiles. Results from the interaction plots, as depicted in *Figure 6 – Figure 17*, show that treatment groups within each quintile are well balanced against each other.

**Figure 5: Distribution of Propensity Score by Quintiles**

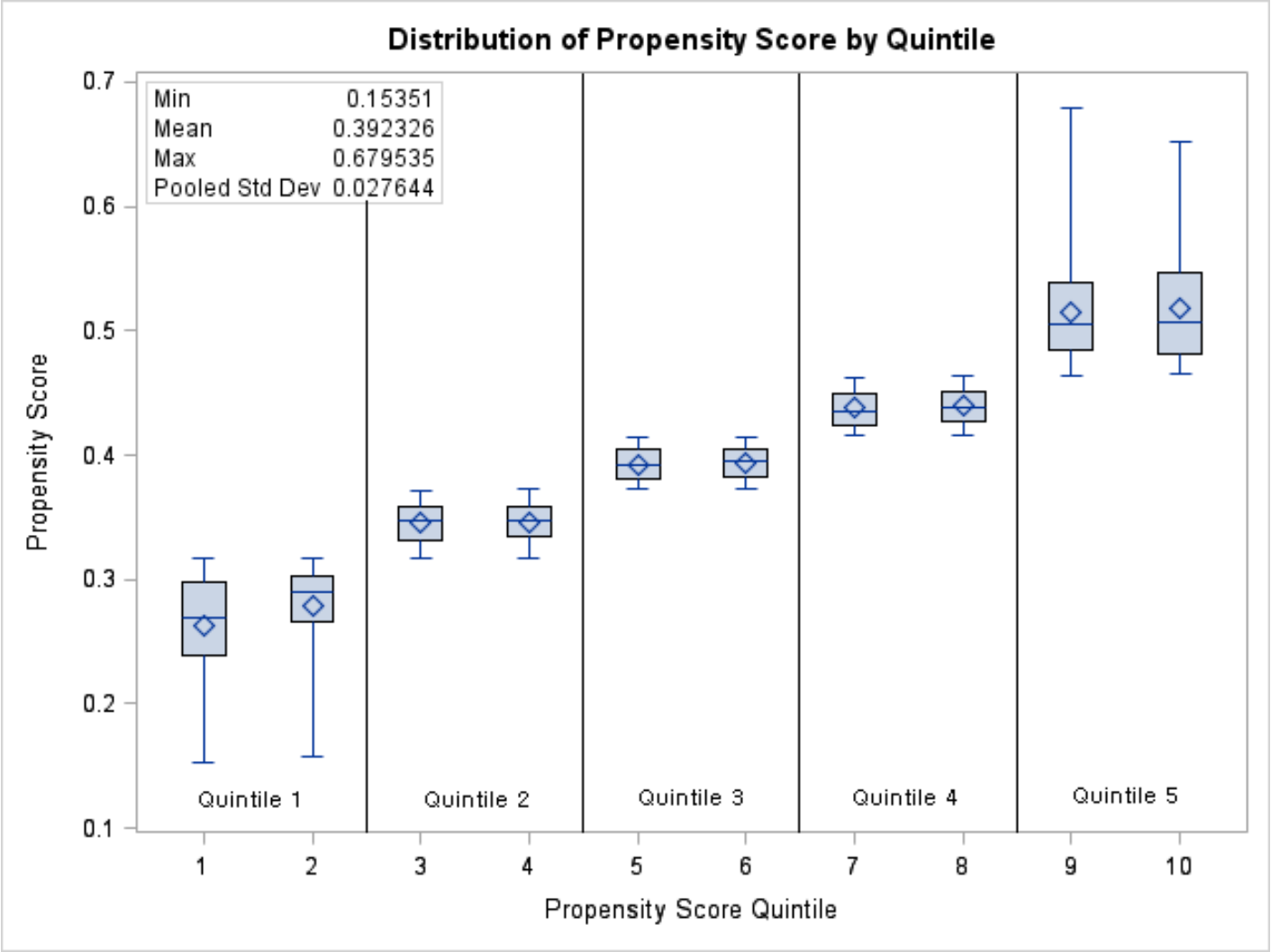


**Table 10: Covariates Balance Before and After Propensity Score**

| | Before | | | After | | |
|---|---|---|---|---|---|---|
| | Treatment Group (Mean) | | | Treatment Group (Least Squared Mean) | | |
| **Variable** | **No Riluzole** | **Riluzole** | **P-Value** | **No Riluzole** | **Riluzole** | **P-Value** |
| Age | 66.63 | 63.36 | <0.0001 | 65.61 | 64.93 | 0.1749 |
| Gender | 1.48 | 1.42 | 0.029 | 1.46 | 1.45 | 0.920 |
| Geographical Location | 7.27 | 7.09 | <0.0001 | 7.21 | 7.18 | 0.882 |
| Marital Status | 0.66 | 0.75 | 0.0005 | 0.69 | 0.69 | 0.944 |
| Availability of Caregiver | 0.83 | 0.86 | 0.099 | 0.84 | 0.84 | 0.971 |
| CPS Scale | 0.61 | 0.48 | 0.0008 | 0.56 | 0.56 | 0.891 |
| ADL Hierarchy Scale | 1.74 | 1.69 | 0.226 | 1.73 | 1.71 | 0.837 |
| IADL Involvement Scale | 11.96 | 12.05 | 0.779 | 11.99 | 12.02 | 0.921 |
| Pain Scale | 1.13 | 1.15 | 0.413 | 1.13 | 1.14 | 0.874 |
| Depression Rating Scale | 1.63 | 1.58 | 0.383 | 1.62 | 1.59 | 0.836 |
| CHESS Scale | 1.65 | 1.62 | 0.176 | 1.64 | 1.63 | 0.925 |
| MAPLe Scale | 3.03 | 2.92 | 0.330 | 2.99 | 2.98 | 0.783 |

**Figure 6: Interaction Plot – Age**

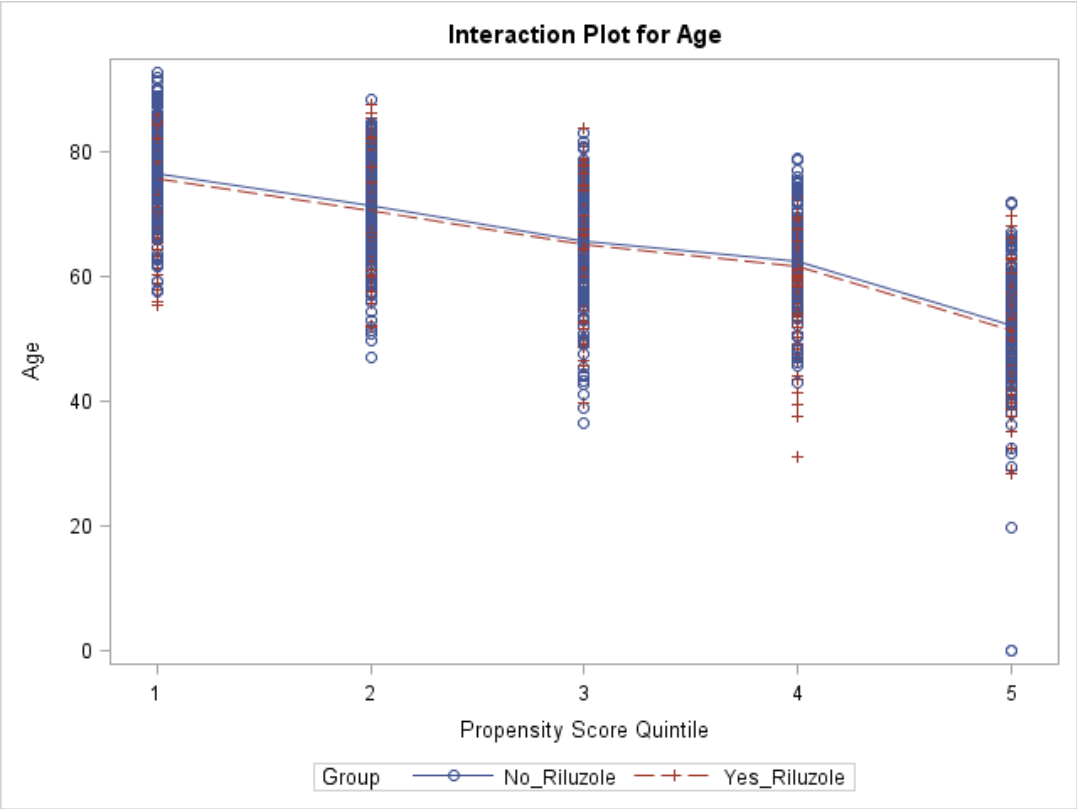



**Figure 7: Interaction Plot - Gender**

**Figure 8: Interaction Plot – Geographical Location**


**Figure 9: Interaction Plot – Marital Status**

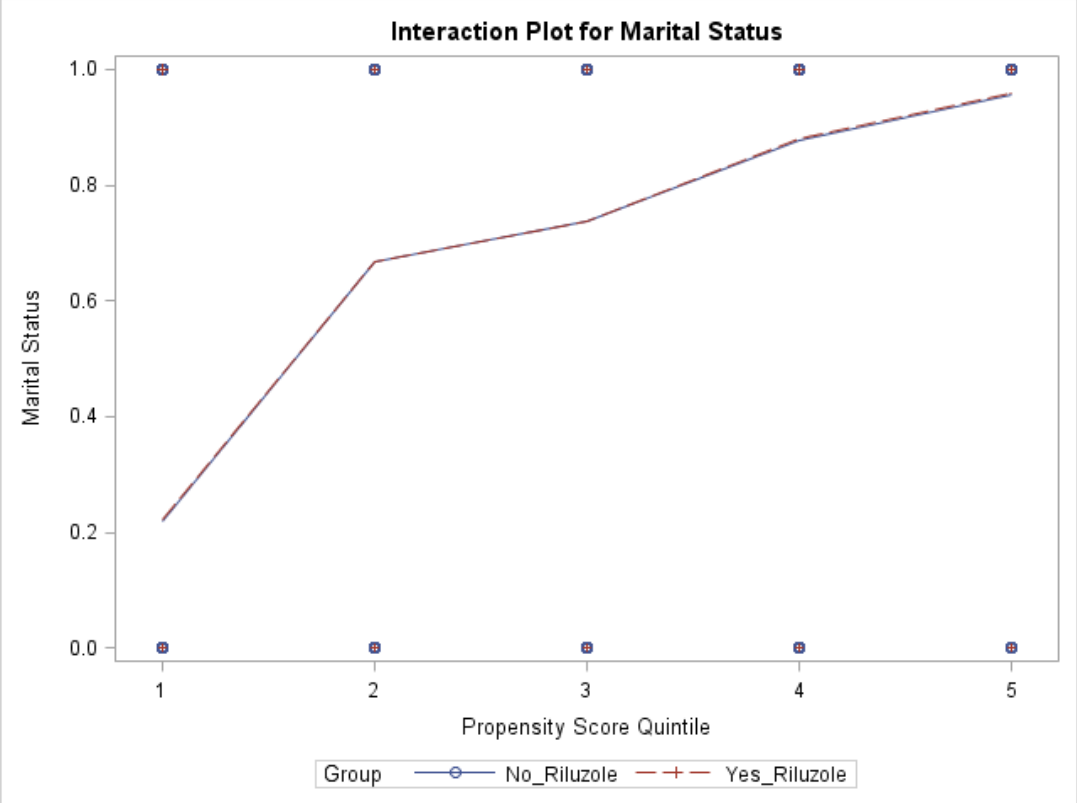


**Figure 10: Interaction Plot – Availability of Caregiver**

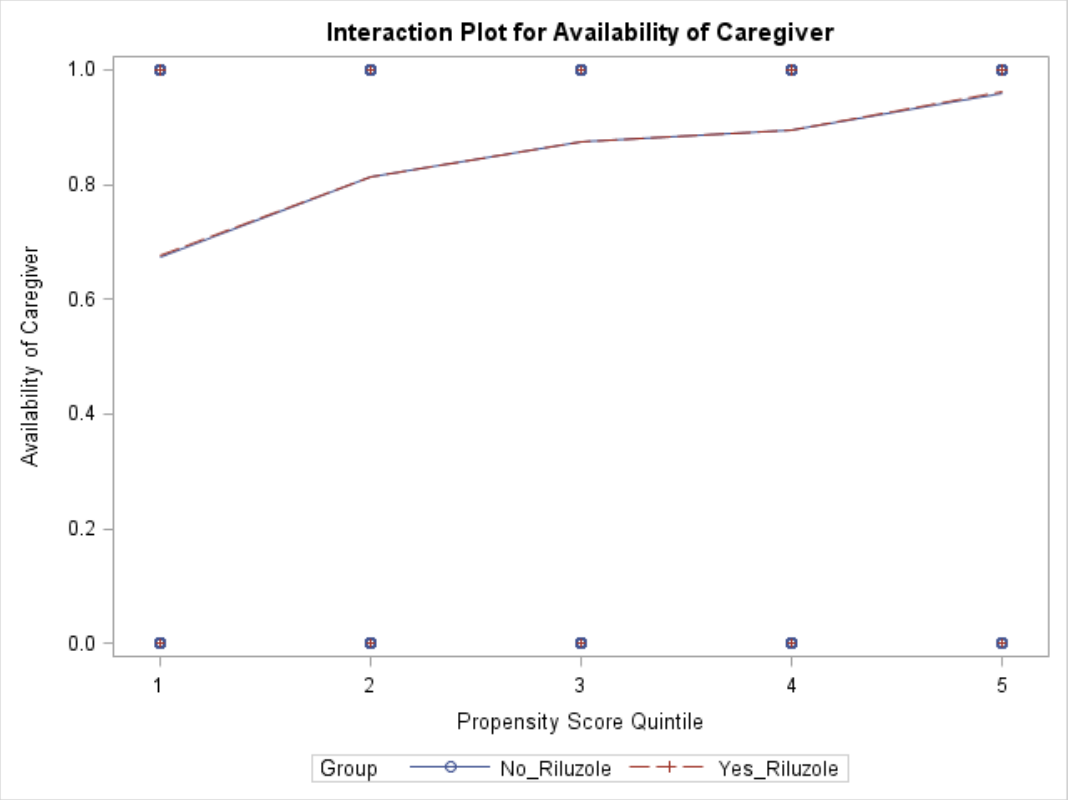



**Figure 11: Interaction Plot – Cognitive Performance Scale**

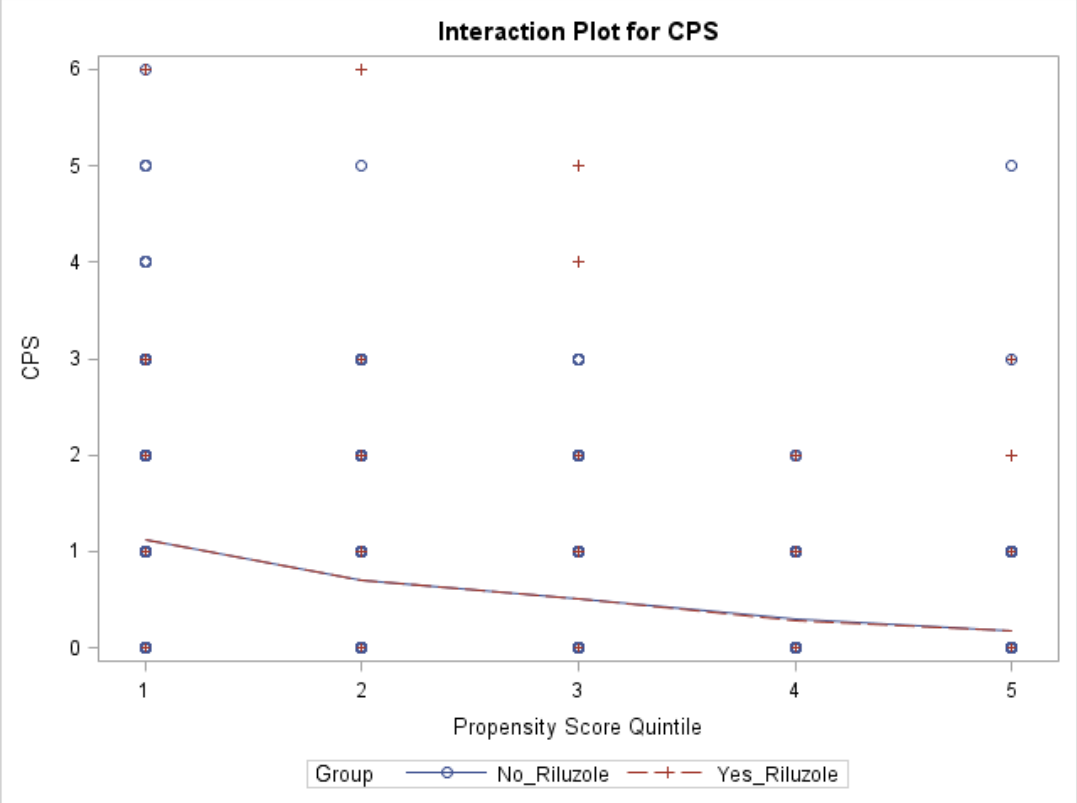


**Figure 12: Interaction Plot – ADL Self-Performance Hierarchy Scale**

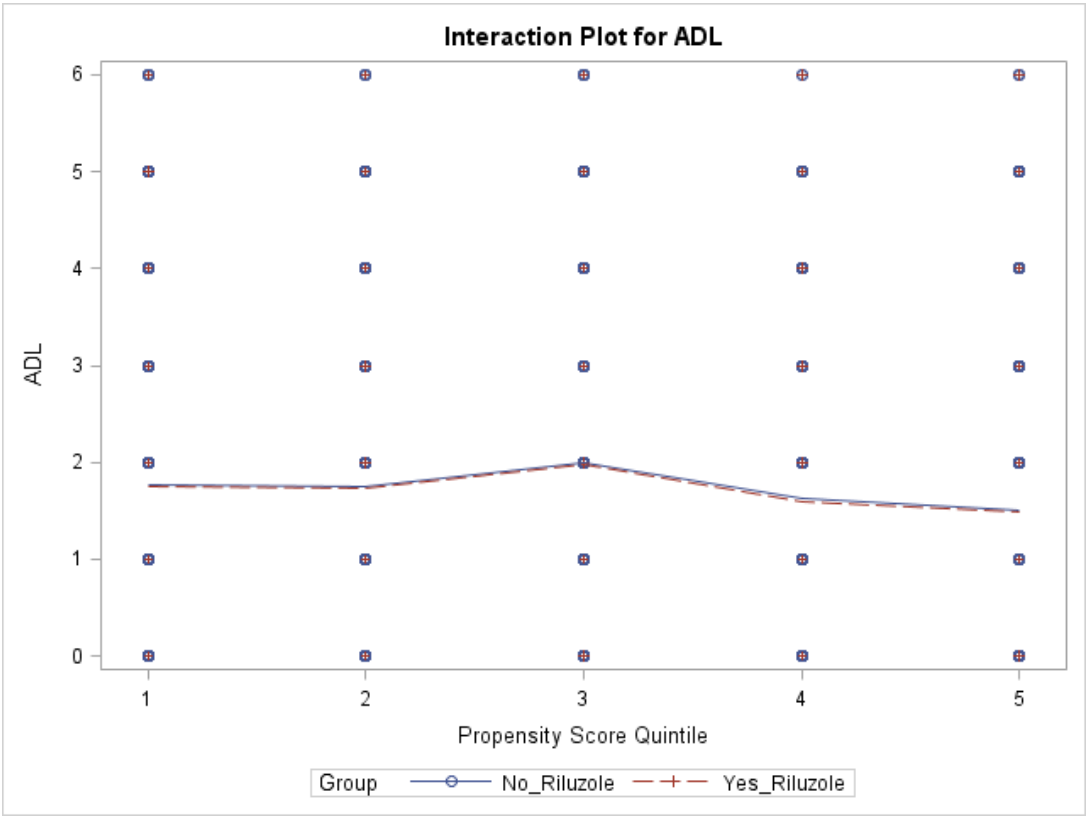



**Figure 13: Interaction Plot – IADL Involvement Scale**

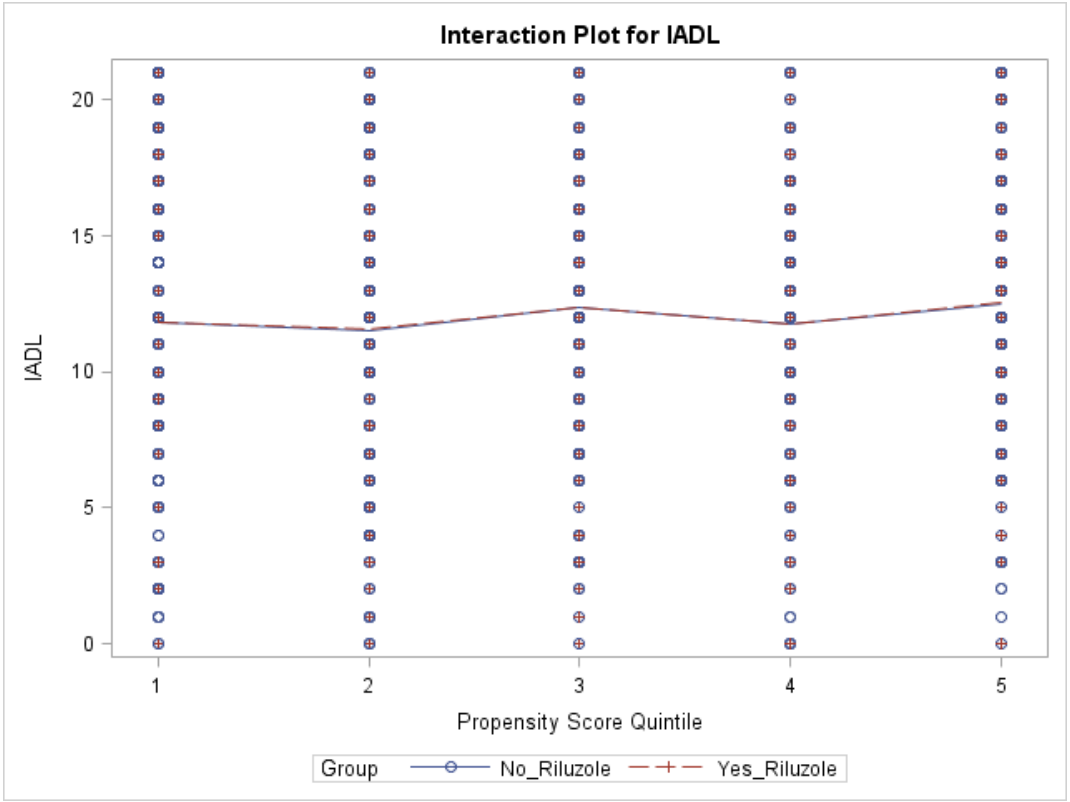


**Figure 14: Interaction Plot – Depression Rating Scale**

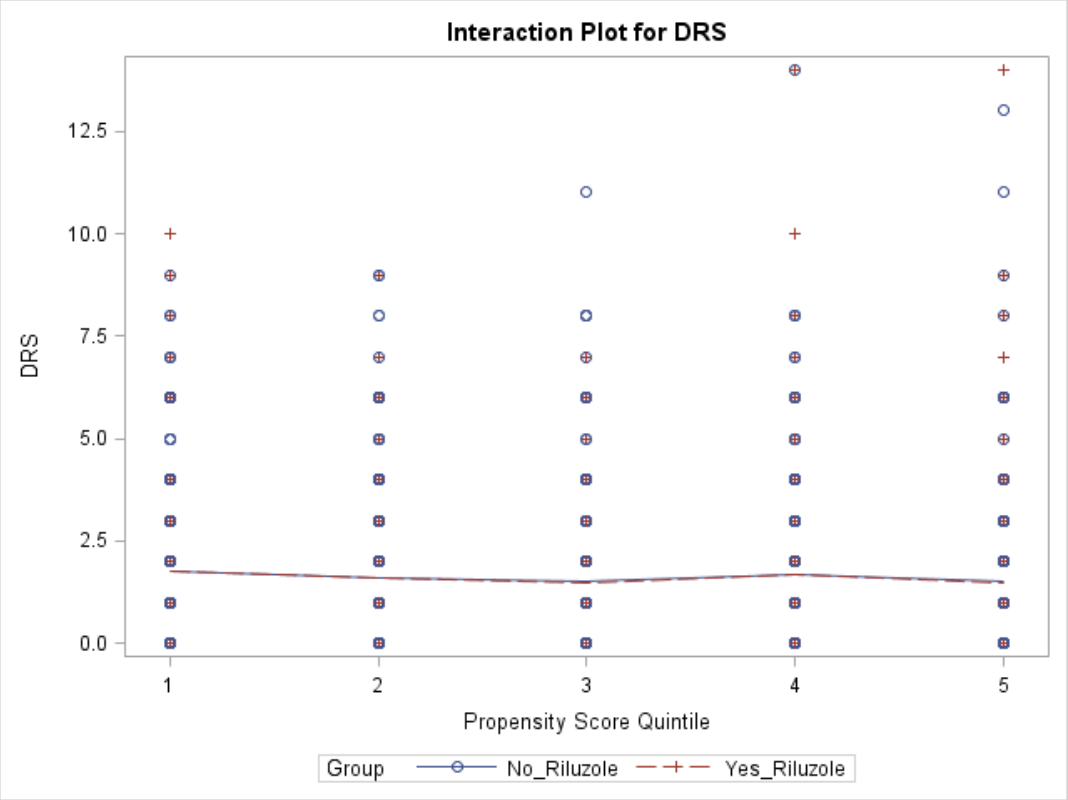



**Figure 15: Interaction Plot – Pain Scale**

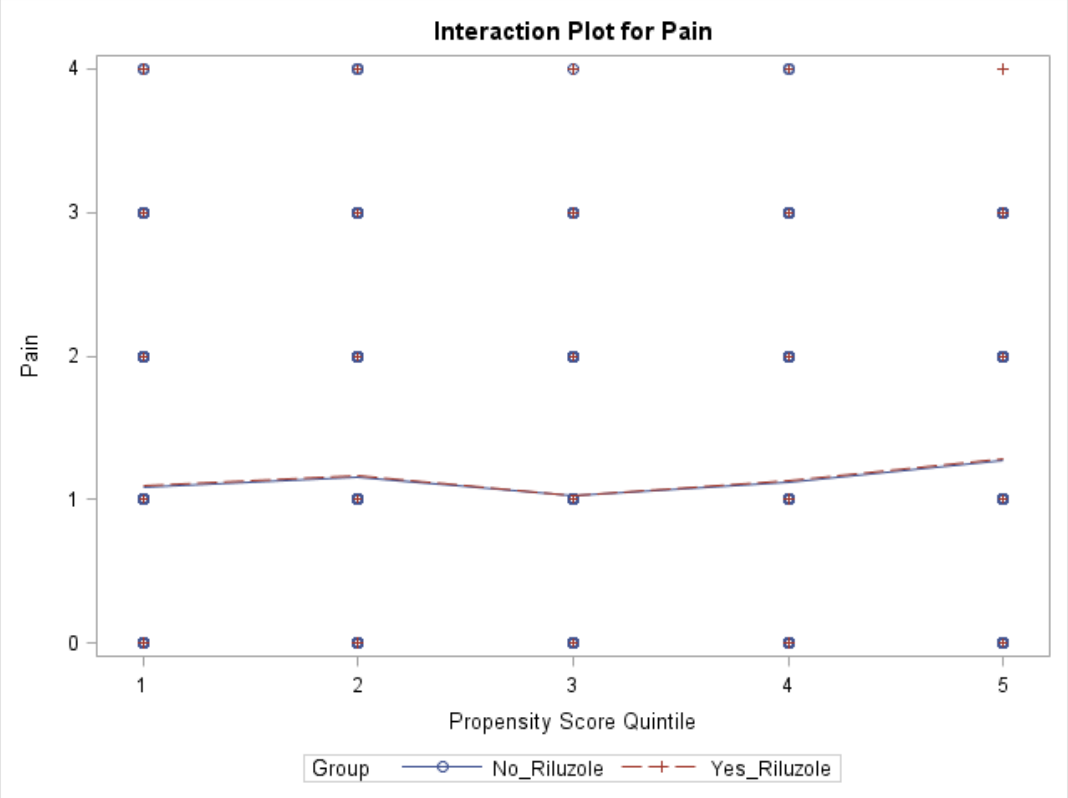


**Figure 16: Interaction Plot – CHESS Scale**

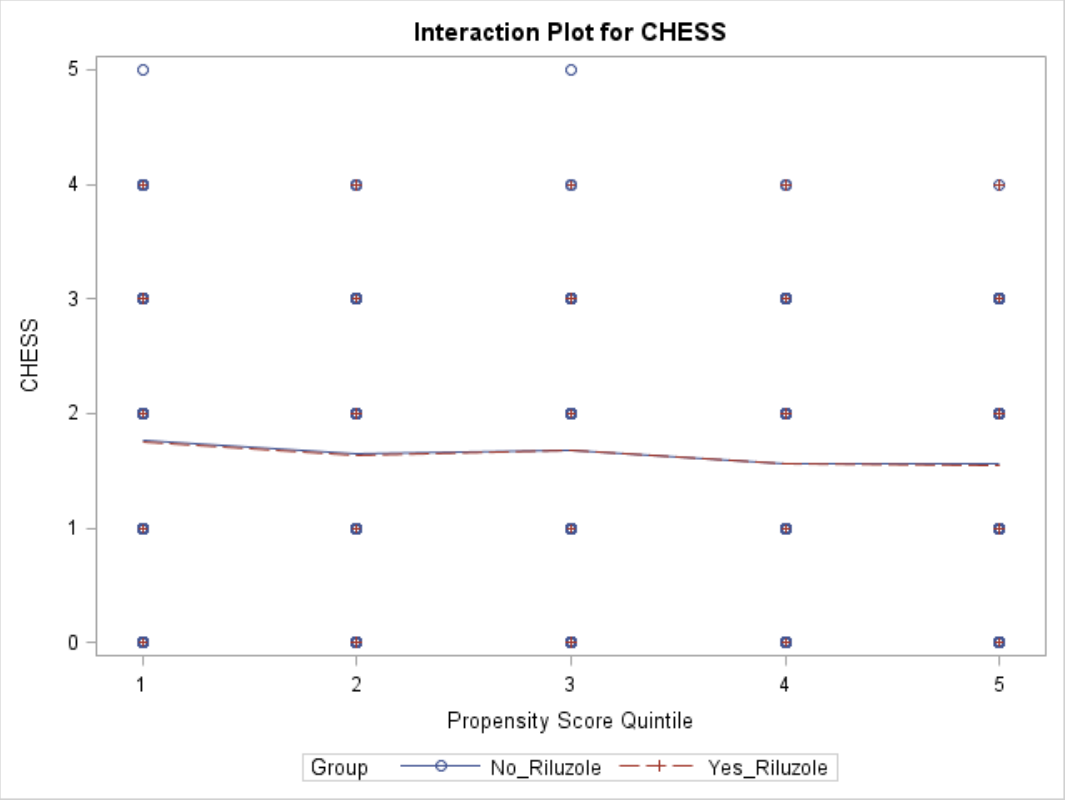
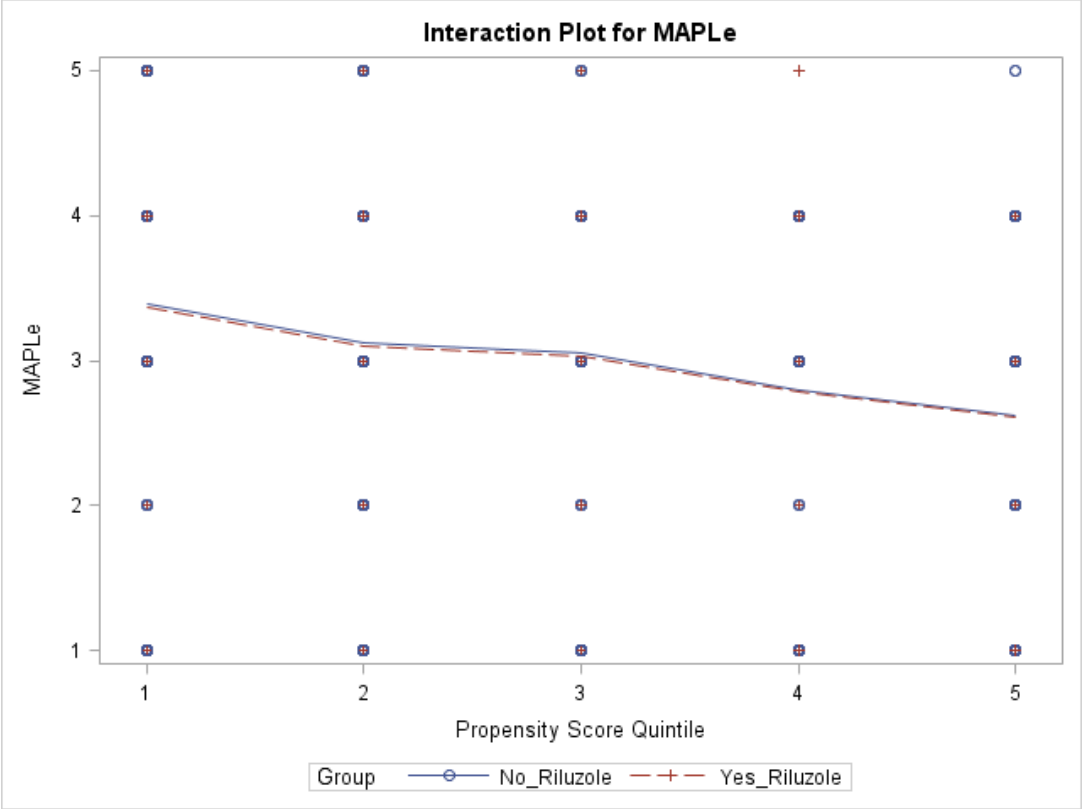



**Figure 17: Interaction Plot – MAPLe Scale**



**Survival Analysis**

Kaplan-Meier survival curves were constructed in order to estimate the stratum-specific average time to discharge. *Figure 18* depicts the stratum-specific Kaplan-Meier survival curves for riluzole and non-riluzole subjects across the five propensity score strata. The stratum-specific survival estimates were used to construct pooled Kaplan-Meier survival curves to estimate the overall measure of treatment effect across the two treatment groups, as shown in *Figure 19*.

The average stratum-specific 2-year mortality (time to discharge) in patients not receiving riluzole was 268, 291, 340, 382, and 360 days for strata 1,3,5,7, and 9, respectively. The average stratum-specific 2-year mortality (time to discharge) in patients receiving riluzole was 305, 342, 342, 380, and 427 days for strata 2,4,6,8, and 10, respectively. The weighted mean of the stratum-specific 2-year mortality for patients not taking riluzole was 321 ± 22 days and 366 ± 25 days for patients taking riluzole. Thus, patients who were taking riluzole, on average, stayed 45 days longer in home care than patients who were not taking riluzole.

When a Cox proportional hazard model that stratified on the five propensity score quintiles was used, the estimated hazard ratio was 0.86 (95% confidence interval: 0.745 – 0.997). Thus, receipt of riluzole reduced the hazard of death, placement into long-term care, and hospitalization by 14%. This effect was statistically significant (p=0.046).

**Figure 18: Stratum-Specific Kaplan-Meier Survival Curve**

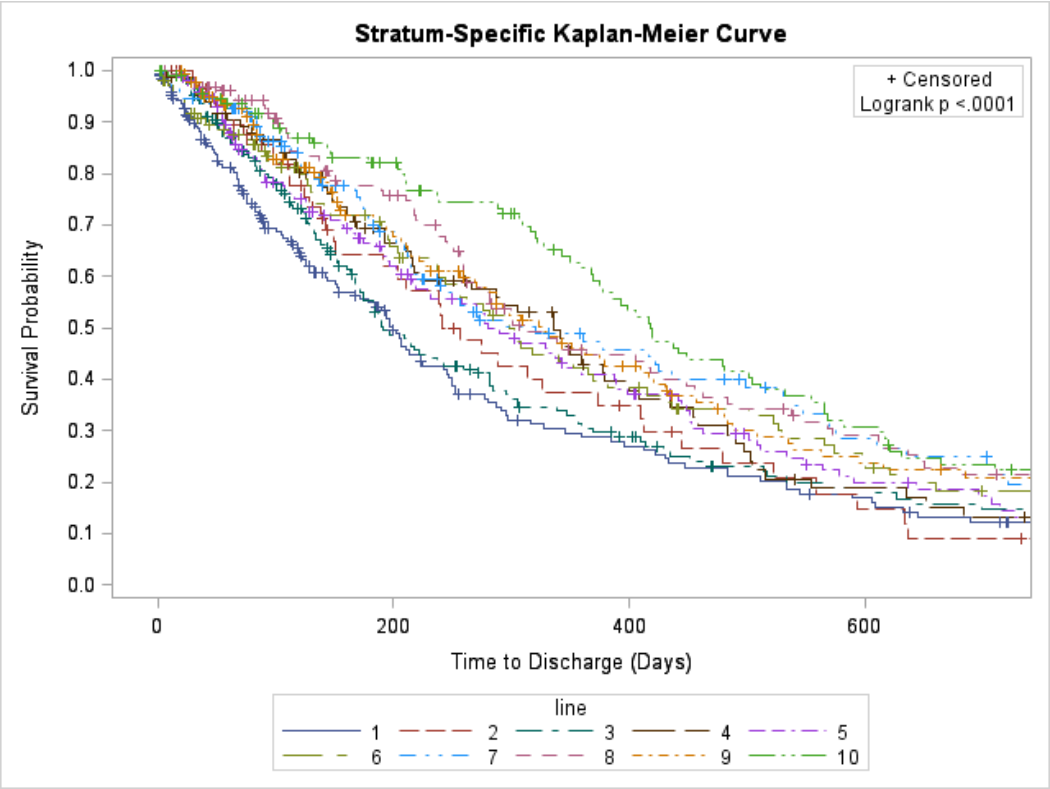
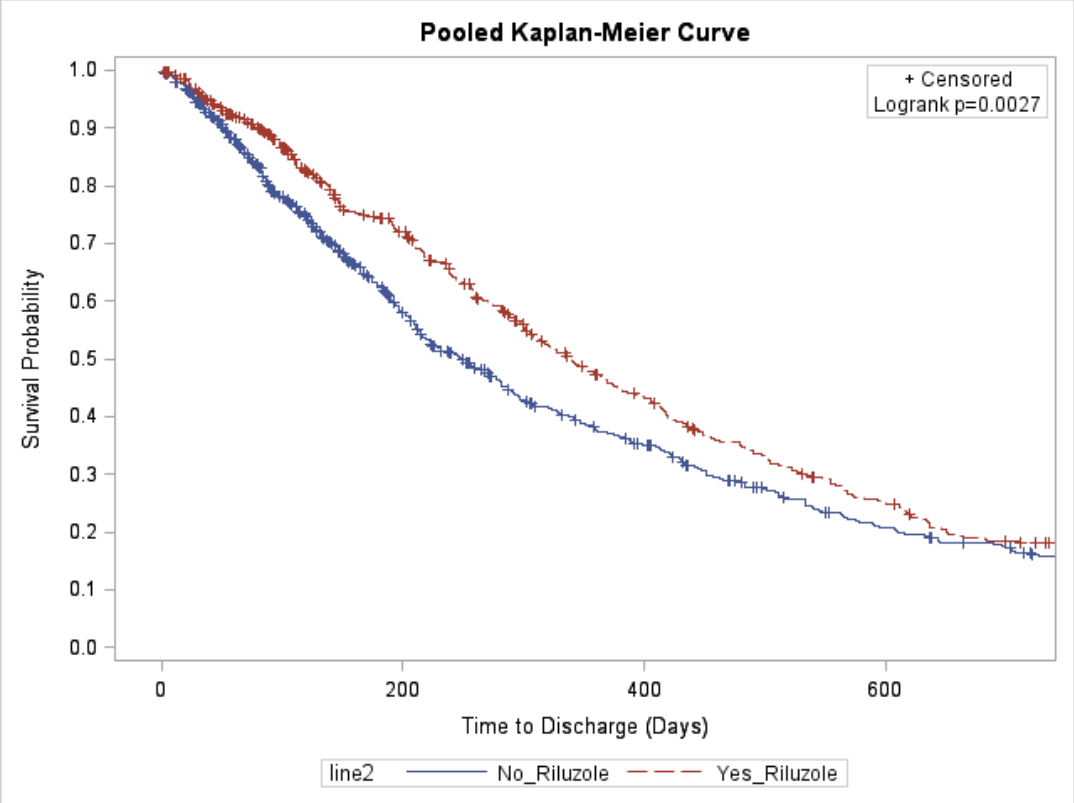



**Figure 19: Pooled Kaplan-Meier Survival Curve**



**Cost Analysis**

A thesis paper by Clare Cheng at the University of Waterloo has estimated that the weekly cost of home care in Ontario for ALS population was $934.96 per week or $48751.49 per year (Cheng, 2013). According to the Ontario Drug Benefits Program, the price of generic versions of riluzole, manufactured by either Apotex Inc., or Mylan Pharmaceuticals Inc. was $7.36 per tablet of 50mg, which results in $14.72 per day in accordance to the recommended dosage per day of 100mg/day. The annual price of riluzole was $5372.80.

While the proportion of the study population discharged to long-term care was equivalent across the two treatment groups, riluzole delayed hospitalization in approximately 3.5% of the total population receiving the drug, which was considered as a cost-offset factor. The cost of hospitalization of ALS was derived from information published in the CIHI patient cost estimator with an estimated average cost of $15,305 per patient per stay. Thus, the cost-saving associated with riluzole in correlation to delay in hospitalization by 45 days for 3.5% of the population receiving the drug was $302.12.

The corresponding ICER was calculated as follows:

**Table 11: Inputs for incremental cost-effectiveness ratio**

| Parameter | Value |
|---|---|
| Cost of Home Care | $48,751.49 |
| Cost of Medication | $5372.80 |
| Hospitalization Cost-Offset | $302.12 |
| Survival Difference | 45 Days |

$$\text{ICER per LYG} = \frac{(48751.49 + 5372.80 - 302.12) - 48751.49}{\frac{45}{365}}$$

The resulting ICER was $41,128.85 per LYG.

In order to calculate the ICER per quality-adjusted life year gained, health utility scores were derived from a previously published literature, which identified stage-specific health utility scores for ALS patients using Amyotrophic Lateral Sclerosis Assessment Questionnaire (ALSAQ-40) and EuroQol EQ-5D (Kiebert et al., 2001). As most patients with ALS in home care were considered to be in mild-moderate stages of ALS, this study assumed a health utility score of 0.74 during the entire duration of the home care stay. In addition, this study assumed that patients in the riluzole group gained additional 45 days, while maintaining a health utility score of 0.74. Furthermore, an assumption was made where patients discharged to long-term care or CCC from both treatment groups would survive equally long with the same quality of life scores.

$$\text{ICER per QALY} = \frac{(48751.49 + 5372.80 - 302.12) - 48751.49}{\frac{45}{365} \times 0.74}$$

The resulting ICER was $55,579.53 per QALY.

**Sensitivity Analysis**

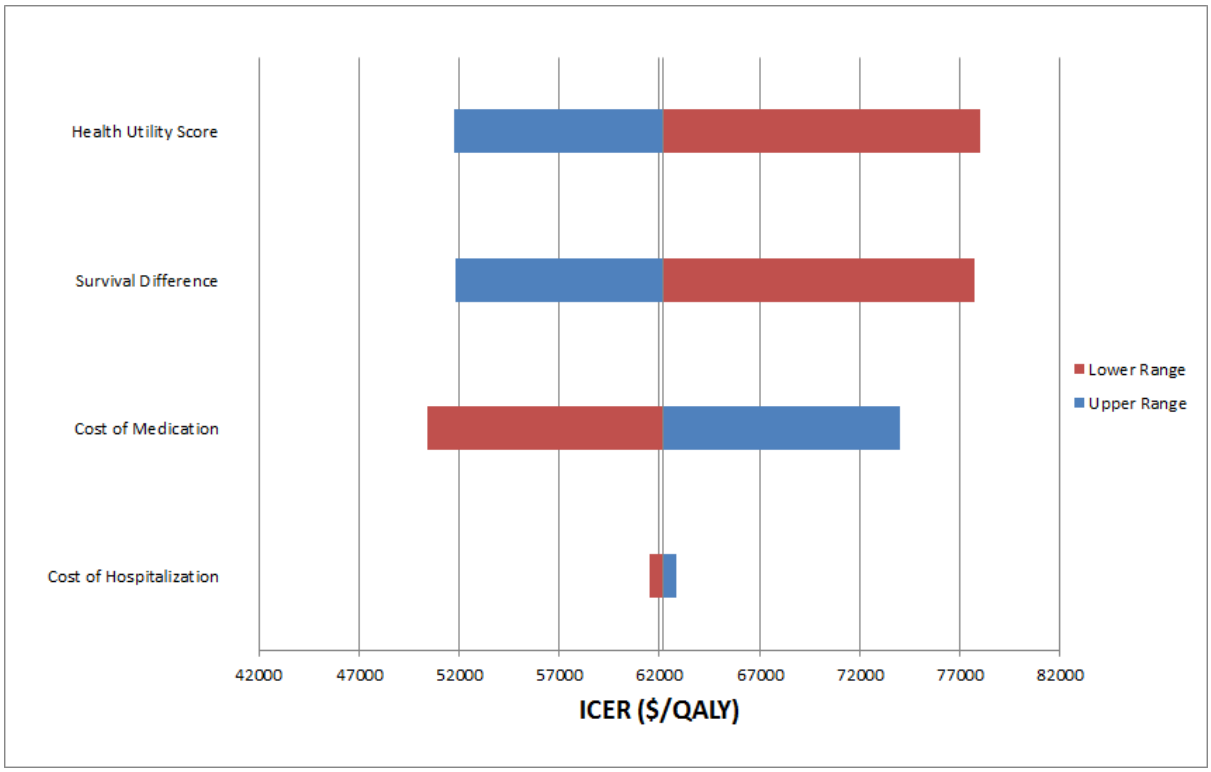
One-way deterministic sensitivity analysis was conducted for the majority of parameters using a range of ± 20% to examine their effects on the ICER. The inputs for the one-way sensitivity analysis are shown in *Table 12*.

The results of the one-way sensitivity analysis are shown in *Figure 20*, which depicts graphically how variations in each parameter affect the ICER. The tornado diagram is stacked in decreasing width, indicating that change in parameter at the top (health utility score) have the greatest effect on the ICER, while change in parameter at the bottom (cost of hospitalization) have the least impact on the ICER.

**Table 12: Inputs for one-way sensitivity analysis**

| Inputs | Base | Upper Range | Lower Range |
|---|---|---|---|
| Cost of Medication | $5372.80 | $6,447.36 | $4,298.24 |
| Health Utility Score | 0.74 | 0.89 | 0.59 |
| Cost of Hospitalization | $302.12 | $362.54 | $241.70 |
| Survival Difference | 45 days | 54 days | 36 days |

**Figure 20: Tornado Diagram**




To estimate how the ICER might change due to alterations in multiple parameters simultaneously, best and worst case scenarios were determined. Inputs included in the scenario analyses involved alterations in all four parameter using the values derived from the one-way deterministic sensitivity analyses. Best case scenario involved upper range values for health utility score & survival differences and lower range values for cost of medication & cost of hospitalization. Worst case scenario involved upper range values for cost of medication & cost of hospitalization and lower range values for health utility score & survival differences. Parameter values for both scenarios are depicted in Table 13.

**Table 13: Inputs for Scenario Analysis**

| Inputs | Base Case | Best Case | Worst Case |
|---|---|---|---|
| Cost of Medication | $5,372.80 | $4,298.24 | $6,447.36 |
| Health Utility Score | 0.74 | 0.89 | 0.59 |
| Cost of Hospitalization | $302.12 | $362.54 | $241.70 |
| Time to Discharge | 45 Days | 54 Days | 36 Days |

**Best Case Scenario:**

$$\text{ICER per QALY} = \frac{(48751.49 + 4298.24 - 362.54) - 48751.49}{\frac{54}{365} \times 0.89}$$

Resulting ICER was $29,890.36 per QALY.

**Worst Case Scenario:**

$$\text{ICER per QALY} = \frac{(48751.49 + 6447.36 - 241.70) - 48751.49}{\frac{36}{365} \times 0.59}$$

Resulting ICER was $106,641.52 per QALY

**5.4 Discussion**

The results of the primary analysis showed that administration of riluzole in patients with ALS in home care involved a cost of approximately $41,000 per life-year gained or $55,000 per quality-adjusted life year gained. Considering that the willingness-to-pay threshold is around $50,000 per QALY, the results of this study suggest an unfavorable cost-effectiveness for riluzole, or at best, a borderline value for cost-effectiveness. However, considering the rare nature of ALS and the fact that riluzole is the only approved medication for the treatment of ALS; the cost implication is not too unreasonable.

Over the course of undertaking deterministic sensitivity analyses, the resulting ICERs ranged from approximately $50,000 per QALY to $78,000 per QALY, reflecting the ICER's sensitivity to parameters of health utility score, survival difference, and the cost of administration of riluzole. In the scenario analyses where multiple parameters were altered simultaneously, the ICERs were $29,890.36 per QALY and $106,641.52 per QALY for the best and worst case scenarios, respectively. Results from the scenario analyses indicate the possibility that riluzole is either cost-effective or exceed the willingness-to-pay threshold.

An interesting finding in the present study was that patients who are older and living alone were less likely to receive riluzole. However, the results from the survival analysis indicated that patients who are older and not married had more to benefit from the use of riluzole.

The present study has several limitations. Firstly, RCTs are the gold standard study design used to accurately assess the efficacy of the drug on outcomes. The random treatment allocation ensures that outcome statuses are not confounded by measured or unmeasured baseline characteristics, which allows the study to estimate the treatment outcome by directly comparing the control and treatment subjects. However, as the OACCAC-HC data is observational, it posed risks of bias as treatment selection may have been influenced by subject characteristics. Although propensity scores were calculated in attempt to minimize the bias, it did not account for bias resulting from the unobserved covariates, which may have influenced treatment selection.

Secondly, as this study only considered initial admission assessments for further statistical analyses, there may have been some bias in the survival estimates. As over 60% of the study population had multiple assessments, it is possible that individuals may not have been on riluzole during their initial assessments, but have been prescribed afterwards. Moreover, as the data do not indicate the initial date of diagnosis for ALS or initial

prescription date of riluzole, it is unclear how long patients had been exposed to the disease or how long they had been on riluzole prior to receiving home care services. Hence, an assumption was made where all ALS patients in home care were in their early stages, which resulted in utilizing a health utility score that corresponded to mild-moderate stages of ALS.

There were other approximations made in the economic estimations for this study. Firstly, cost of hospitalization for ALS patients in Canada was not available. The cost was derived from the CIHI patient cost estimator – Neuromuscular disorder, as information on ALS case mix group was not available in the CIHI-PCE. Therefore, neuromuscular disorder case mix group was chosen as it was the most relevant disease category next to ALS. Furthermore, an assumption was made where both treatment groups would survive equally long with the same utility score after discharging from home care. Thus, the cost of hospitalization and the utility score was assumed to be the same for the two treatment groups.

The results of this study differ from results found in the four previous cost-effectiveness analyses of riluzole. In the two studies conducted by Ginsberg & Lev and Tavakoli et al., riluzole was found to be cost effective with ICERs of $12,013 USD ($15,743 CAD) per LYG or $18,027 USD ($23,612 CAD) per QALY and $20,908 USD ($27,401 CAD) or $28,451 USD ($37,286 CAD) per QALY, respectively. On the other hand, studies conducted by Messori et al., and Gray found riluzole to be not cost effective with ICERs of $62,609 USD ($82,052 CAD) per LYG or $90,514 USD ($118,623 CAD) per QALY and $49,200 USD ($64,479 CAD) per LYG or $73,416 USD ($96,215 CAD) per QALY, respectively.

One possible reason for the difference in the ICER estimates may be due to the variations in the survival estimates. For example, the present study found that riluzole was associated with 1.5 months of survival gain in home care, which is relatively less compared to the study conducted by Tavakoli et al., which reported that riluzole was associated with 6.3

months of survival gain. Ginsberg & Lev estimated that riluzole prolonged life by approximately 3 months, while Gray reported that riluzole was associated with additional 1.1 months in survival gains.

Another possible reason may be the health utility scores that were used to develop the ICERs per QALY. The present study assumed utility score of 0.74 for both treatment groups during the entire duration of home care stay as no information on disease stages were available. However, other studies have examined the benefits associated with riluzole over the entire course of the disease, incorporating stage-specific utility scores.

Lastly, the differences in the ICERs may well be explained by the components included in the cost analysis. As this study solely focused on ALS patients in home care setting, direct costs included standard supportive care, medication, and cost-savings from delay in hospitalization. However, as other studies have conducted cost-analyses accounting for the entire course of the disease, cost components included costs of outpatient visits, ALT testing, and medical procedures such as tracheostomy, jejunostomy, and gastrostomy, which are all relevant for patients who are in more advanced stages of ALS. Furthermore, it is important to note that previous studies were conducted in different parts of the world (Italy, Israel and UK). Therefore, the cost of administration of riluzole and the types of medical services in routine clinical practice may differ in different countries.

It is worth mentioning that this study was the first of its kind conducting cost-effectiveness of riluzole using an observational database. The present study benefitted from the total sample of 1,351 populations, which is by far the largest cohort size that was used to assess the cost-effectiveness of riluzole. However, figures presented in this study are only illustrative rather than an exact measurement and thus, these results should only be used as a guide to aid in the decision-making process. With an ICER of $55,579.53 per QALY, cost-effectiveness of riluzole is not too unreasonable considering the fact that it is a therapeutic

area with relatively small numbers of patients and where no alternative therapy exists.

Future studies should investigate the cost-effectiveness of riluzole in nursing homes and complex continuing care using observational data to better understand the benefits associated with riluzole in more advanced ALS patients. Moreover, direct costs and indirect costs associated with the management of ALS in Canada should be quantified. Lastly, information on quality of life in correlation to disease progressions should be better understood in order to accurately assess the cost-effectiveness of riluzole.

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# APPENDICES

**APPENDIX A: Management and Assistance**

| Stage | Effects | Supportive Treatment | Time spent in stage (median duration in months) |
|---|---|---|---|
| **1** | - Muscle cramping and fasciculation<br>- Fatigue, poor balance, slurred speech, weak grip, tripping during walking | - Help with minor physical tasks<br>- Tools & devices (canes, leg brace) to aid daily functions | 18.1 |
| **2** | - Muscle paralysis<br>- Contractures and joint pain<br>- Chocking and difficulty eating from weakness in swallowing muscles<br>- Respiratory insufficiency from weakness in breathing muscles | - Range-of-motion exercise to help keep joints limber<br>- Splints to help extremities remain stretched<br>- Feeding tubes<br>- Noninvasive ventilation<br>-Equipment to aid physical function (e.g. wheelchair) | 5.5 |
| **3** | - Muscle paralysis (all voluntary muscles)<br>- Unable to breathe without ventilator<br>- Fatigue, headaches, and susceptibility to pneumonia<br>- Unable to speak<br>- Eating and drinking are impossible by mouth | - Motor wheelchair<br>- Hospital bed<br>- Mechanical lift<br>- Communication devices<br>- Noninvasive or invasive (tracheostomy) ventilation<br>- Feeding tube<br>- Urinary catheters | 6.7 |
| **4** | - Disability to use lung muscles<br>- Inability to swallow from swelling of passage ways | | 5.9 |

*(Charpentier, 2015)*

**APPENDIX B: History of Rilutek®**

| DATE | DESCRIPTION |
|---|---|
| **DECEMBER, 1995** | Rhone-Poulenc Rorer, Inc. acquired approval of Rilutek® (Riluzole) from FDA. |
| **JANUARY, 1999** | Rhone-Poulenc Rorer, Inc. merged with Hoescht AG to form Aventis, Ltd. |
| **JANUARY, 2003** | Implax Labs acquired FDA approval of its generic version of Rilutek-50mg, but has been unable to sell the product since that time due to an injunction entered in patent litigation with Aventis. |
| **AUGUST, 2004** | Aventis, Ltd. merges with Sanofi-Synthélabo to form Sanofi-Aventis. |
| **APRIL, 2013** | Switzerland-based specialty pharmaceutical company, Covis Pharma Sarl, announced its agreement with Sanofi-Aventis U.S. LLC to acquire rights to Rilutek |
| **JUNE, 2013** | Patent expiration of Rilutek.<br>FDA granted approval to three companies to market generic versions of Riluzole (Sun Pharmaceutical Industries Ltd., Apotex Inc., and Glenmark Generics Inc.) |
| **JULY, 2013** | FDA granted approval to Mylan Pharmaceuticals Inc. to market generic version of Riluzole |
| **MARCH, 2016** | FDA granted approval to Alkem Labs Ltd. to market generic version of Riluzole |

**APPENDIX C: Literature Review Search Strategy**

**Inclusion Criteria:**

**INCLUSION CRITERIA**

| | |
|---|---|
| **POPULATION** | Patients diagnosed with ALS |
| **INTERVENTION** | Administration of riluzole with an objective to delay the onset of ventilator-dependence or tracheostomy-free survival |
| **COMPARATORS** | All comparators were considered eligible for inclusion, including any of the interventions in comparison with each other or versus no treatment or usual supportive care therapy |
| **OUTCOMES** | Cost effectiveness (both incremental cost and incremental effectiveness) was included |
| **DESIGN** | Economic evaluation: cost-effectiveness, cost-utility, cost-benefit, cost-minimization, cost-consequence were all considered eligible. |

**Search strategy for literature review:**

| |
|---|
| ***PubMed*** |
| **Search (cost effective* OR cost analysis OR cost utility OR cost benefit analysis OR economics OR pharmacoeconomics OR quality-adjusted life year OR survival gain* OR drug costs OR costs and cost analysis OR cost OR costs) AND (riluzole OR rilutek) Filters** |
| ***Scopus*** |
| **( TITLE-ABS-KEY ( cost OR costs OR "quality adjusted life year" OR "cost effective" OR economics OR pharmacoeconomics OR economic* OR "survival gain*" OR "cost utility" OR "cost benefit" ) AND TITLE-ABS-KEY ( riluzole OR rilutek ) ) AND ( LIMIT-TO ( LANGUAGE , "English" ) )** |

**APPENDIX D: Care Facilities**

| | Home Care (HC) | Nursing Home (NH / LTC) | Complex Continuing Care (CCC) |
|---|---|---|---|
| **Description** | Care facility publicly funded in Ontario that provides assistances in health and social services to help patients with health conditions that prohibits them from carrying on their normal activities of daily living. Home care is mainly focused on prevention and maintenance and can be a substitute for acute-care or long-term care facility. | Care facility specifically designed for patients with complex medical needs who require supportive living and 24 hour on-site nurse assessments. Most patients in LTC are those with health conditions that undergo frequent fluctuation and require immediate health professional assessments. | Care facility for patients whose current health conditions cannot be cared for in the community or long-term care facility. CCC is designed as a time–limited in-hospital care to help with complex disease management and restorative care. Moreover, CCC provides supportive end-of-life care to optimize quality of life of patients with chronic health conditions. |
| **Service Provision** | - Nursing services<br>- Physiotherapy<br>- Occupational therapy<br>- Speech therapy<br>- Social work services<br>- Dietitian services<br>- Personal support services | - Nursing services (24 hour on-site)<br>- Tailored personal support based on patients' assessed needs<br>- Medical management<br>- Wound care<br>- Social work services<br>- Accommodation and furnishing<br>- Meals and housekeeping recreation<br>- Medication management<br>- Rehabilitation services<br>- Dietitian services<br>- End of life care needs | - Complex medical service<br>- Rehabilitation service<br>- Palliative care service<br>- Respite service<br>- Nursing aide<br>- Therapeutic services<br>- Technological services<br>- Recreation therapy<br>- Physiotherapy<br>- Occupational therapy<br>- Speech language pathology<br>- Spiritual care<br>- Nutritional services<br>- Personal support services<br>- Social work services<br>- Wound care |
| **ALS Stage** | Mild (1) to Moderate (2) | Severe (3) to Palliative (4) | Severe (3) to Palliative (4) |

**(**Gaugler, 2004; Hirano, 2003; MacAdam, 1993)

**APPENDIX E: CCAC/LHIN Map**


(Community Care Access Centres, n.d.)

1. Erie St. Clair
2. South West
3. Waterloo Wellington
4. Hamilton Niagara Haldimand Brant
5. Central West
6. Mississauga Halton
7. Toronto Central
8. Central
9. Central East
10. South East
11. Champlain
12. North Simcoe Muskoka
13. North East
14. North Wes