NEGOTIATING A PROGRESS PARADOX:
THE VALUE OF EXERCISE FOR PEOPLE LIVING WITH AMYOTROPHIC LATERAL SCLEROSIS

by

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Abstract

Amyotrophic lateral sclerosis (ALS) is a progressive and fatal neuromuscular disease that leads to the paralysis of voluntary muscles used for walking, talking, eating and breathing. There is no cure for ALS and current treatments, including exercise therapies, are extremely limited (Kiernan et al., 2011). The first of two studies presented herein aimed to examine the tolerance and training effects of modified sprint interval training (SIT) for people with ALS. Despite an available population and persistent efforts, one participant completed the training study over eighteen months. For this individual, SIT was well tolerated acutely and chronically, and functional capacity and aerobic fitness were unchanged following six weeks of home-based SIT training. The inability to recruit sufficient participants for this intervention trial called into question how individuals living with ALS negotiate exercise and barriers to participation.

A second study guided by interpretive phenomenology used in-depth interviews to better understand how everyday experiences of living with ALS impact the ways individuals with ALS engaged with physical activity and exercise. From the subjective accounts of seven men and women living with ALS in Southeastern Ontario, three major themes were identified: 1) living in a changing body, 2) environmental access and 3) the (f)utility of exercise, which speak to the complex process of negotiating the value of exercise for a body that is progressively and incurably deteriorating. Findings suggest there is immense variability and individuality amongst people with ALS and their experiences and attitudes towards physical activity and exercise. Numerous physical, psychological and environmental barriers were also found to be common to people with ALS and may serve as targets to be addressed by future customized exercise interventions.

Dedication

I have endless gratitude for the eight individuals who shared their time, stories and experiences that contributed to this thesis. My understanding of ALS has been forever changed by each of you.

Acknowledgements

I would like to extend my sincerest gratitude to Dr. Brendon Gurd, Dr. Matti Allen and Dr. Sean Taylor, it was a privilege to benefit from your mentorship. Brendon, thank you for your sound advice, feedback and willingness to support an endeavor outside your area of expertise. I appreciate your humour, guidance and reassurance when I had my doubts. Thank you, Matti, for your thoughtful check-ins, diligent revisions and genuine support over the last two years. I admire your positivity, approachability and work ethic. Sean, thank you for graciously tolerating a human shadow, connecting me with participants and allowing me to gain valuable insight to the clinical treatment of ALS.

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List of Abbreviations

ALS- Amyotrophic Lateral Sclerosis

ALSFRS-R- Revised Amyotrophic Lateral Sclerosis Functional Rating System

EMG- Electromyography

END- Endurance

FSS- Fatigue Severity Scale

HCP- Healthcare Professional

HR- Heart Rate

HRR- Heart Rate Reserve

LMN- Lower Motor Neuron

MN- Motor Neuron

MND- Motor Neuron Disease

PSW- Personal Support Worker

QoL- Quality of Life

RCT- Randomized Controlled Trial

RPE- Rating of Perceived Exertion

RPM- Revolutions Per Minute

SIT- Sprint Interval Training

SMEP- Strictly Monitored Exercise Program

UCP- Usual Care Program

UMN- Upper Motor Neuron

VAFS- Visual analogue fatigue scale

VO_2 peak- Peak Volume of Oxygen

8UG- 8-foot Up and Go Test

Chapter 1

Introduction

1.1 General Introduction

The present thesis examines the potential role of exercise in the lives of people living with amyotrophic lateral sclerosis (ALS), a disease that leads to the paralysis of voluntary muscles used for walking, talking, eating and breathing. There is no cure for ALS and current treatments are extremely limited (Kiernan et al., 2011). Exercise as a therapeutic strategy is safe and modestly beneficial for people with ALS (Dal Bello-Haas et al., 2007; Drory et al., 2001; Lunetta et al., 2016), however, traditional long duration aerobic exercise can be difficult because of respiratory weakness and general fatigue (Sharma et al., 1995). The first of the two studies included in the current thesis aimed to investigate the tolerance and utility of modified sprint interval training where short effortful intervals are separated by periods of rest. It was hypothesized that this modality of exercise would be better tolerated, and thus be potentially more suitable than, endurance training for people with ALS. However, despite an available population of ALS patients and persistent recruitment efforts only one participant was successfully recruited and completed the study over the past 18 months. The failure to sufficiently recruit for this intervention study led to the formulation of questions surrounding how people with ALS negotiate exercise engagement as experts of their own experience. Using a drastically different methodology, the second study in this thesis was guided by phenomenology and used in-depth interviews to better understand how everyday experiences of living with ALS impact the ways individuals engage with physical activity and exercise. The findings of the present thesis identify important considerations for future research and interventions seeking to support individuals with ALS and ensure that these individuals derive value and benefits from exercise and physical activity.

1.2 Thesis Organization

In Chapter 2 the reader will find a background of ALS including basic neuromuscular physiology, disease pathophysiology, clinical symptomology and currently available treatments. Following an explanation of disease progression, the relevance of exercise as a therapeutic strategy will be explored through a detailed review of the literature concerning exercise and ALS in animal and human models. Chapter 3 contains a manuscript examining the tolerance and training effects of a modified sprint interval stair stepping protocol for one participant with ALS. Chapter 4 provides a reflection of the unsuccessful intervention study and transitions towards a qualitative approach by introducing the reader to the usefulness of exploring individual experience from a paradigm that attends to complexities and difference. A brief review of the literature concerning chronic illness and phenomenological investigations in motor neuron disease and ALS are also provided here. The manuscript in Chapter 5 examines the everyday experiences of people living with ALS and the ways they negotiate engagement in physical activity and exercise. Chapter 6 offers a discussion of key findings of the thesis, a critical examination of the call for further randomised controlled trials in the population, strengths, limitations and future directions. Finally, a detailed appendix is attached to provide more thorough details of items discussed within the thesis.

1.3 References

Dal Bello-Haas, V., Florence, J., Kloos, A., Scheibecker, J., Lopate, G., Hayes, S., … Mitsumoto, H. (2007). A randomized controlled trial of resistence exercise in individuals with ALS. *Neurology*, *68*, 2003–2007.

Drory, V. E., Goltsman, E., Reznik, J. G., Mosek, a, & Korczyn, a D. (2001). The value of muscle exercise in patients with amyotrophic lateral sclerosis. *Journal of the Neurological Sciences*, *191*(1–2), 133–137. https://doi.org/10.1016/S0022-510X(01)00610-4

Kiernan, M. C., Vucic, S., Cheah, B. C., Turner, M. R., Eisen, A., Hardiman, O., … Zoing, M. C. (2011). Amyotrophic lateral sclerosis. *The Lancet*, *377*(9769), 942–955. https://doi.org/10.1016/S0140-6736(10)61156-7

Lunetta, C., Lizio, A., Sansone, V. A., Cellotto, N. M., Maestri, E., Bettinelli, M., … Corbo, M. (2016). Strictly monitored exercise programs reduce motor deterioration in ALS: preliminary results of a randomized controlled trial. *Journal of Neurology*, *263*(1), 52–60. https://doi.org/10.1007/s00415-015-7924-z

Sharma, K. R., Kent-Braun, J. a, Majumdar, S., Huang, Y., Mynhier, M., Weiner, M. W., & Miller, R. G. (1995). Physiology of fatigue in amyotrophic lateral sclerosis. *Neurology*, *45*(4), 733–740. https://doi.org/10.1212/WNL.45.4.733

Chapter 2

Literature Review

2.1 Introduction

Amyotrophic lateral sclerosis (ALS; also known as Lou Gehrig's disease) is a progressive and fatal neurodegenerative disease of the human motor system (Kiernan et al., 2011). The prognosis is rapid and relentless, featuring weakness, wasting and subsequent paralysis of voluntary muscles (Swash & Desai, 2000). Within three years of diagnosis, most patients lose the ability to control voluntary movement, swallow food, and breathe without ventilator assistance (Gubbay et al., 1985). The average length of survival is three to four years from symptom onset and only 4% of patients with ALS survive 10 years or longer (Chio et al., 2013).

Relatively rare, ALS affects about 4-7.8 per 100,000 individuals in Europe each year, with 1-3 per 100,000 new cases annually (Chio et al., 2013). While epidemiological data specific to ALS in Canada is incomplete, available rates of incidence and prevalence in Canada's eastern provinces are consistent with European figures (Wolfson, Kilborn, Oskoui, & Genge, 2009). Incidence rates increase with age in both men and women between the ages of 40 and 75 years (Logroscino et al., 2010) and the median age of onset is 55 years (Swash & Desai, 2000). Most cases of ALS are considered sporadic (i.e. of unknown cause) while 5-10% are hereditary, termed familial ALS (Pasinelli & H. Brown, 2016). Importantly, neither is clinically distinguishable from the other, and both are closely associated with rapid functional decline and decreasing quality of life.

2.2 Neuromuscular Physiology

ALS pathologically affects cells responsible for connecting the central nervous system with skeletal muscle, known as motor neurons (MN). There are two classes of motor neurons involved in relay-style voluntary control; upper motor neurons (UMN) found in the cerebral cortex and brainstem, and lower motor neurons (LMN) whose cell bodies are found in the brainstem and spinal cord (J. Ravits, Laurie, Fan, & Moore, 2007). An UMN communicates with its LMN through chemical synapse by releasing the neurotransmitter glutamate to act upon specialized receptors. Once the LMN has received enough excitatory input to surpass its firing threshold, long axons of the LMNs then carry electrical impulse messages (action potentials) to the associated muscle (MacIntosh, Gardiner, & McComas, 2006), see figure 1. The point of communication between the motor neuron and muscle fiber is called the neuromuscular junction where acetylcholine is released from the LMN axon terminal and binds to a specialized receptor on the muscle fiber to initiate contraction (MacIntosh et al., 2006) (see figure 2). Voluntary muscle contraction is therefore highly dependent on the collective health and function of UMNs, LMNs and muscle fibers.

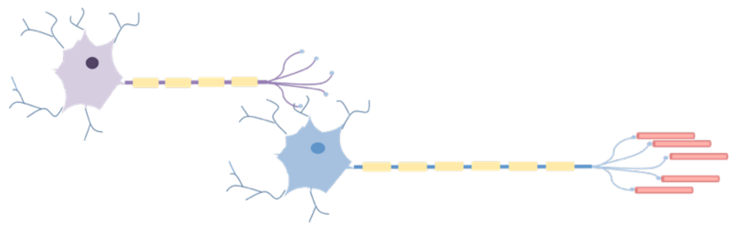

Figure 2. Schematic of upper motor neuron (purple) synpasing on lower motor neuron (blue)

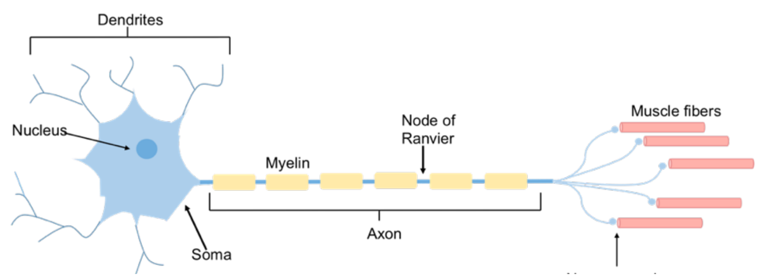

Figure 1. Labelled segments of a lower motor neuron

Characteristics like force production and muscle size are influenced by the relationship between the LMN and the muscle fibers they innervate. One LMN innervates many muscle fibers within the same muscle belly, this is called a motor unit (MU; Burke, 2011). MUs vary in size depending on the number of fibers innervated by a single motor neuron, and each MU contracts in an all-or-none fashion when the motor neuron fires (Mendell, 2005). As figure 3 illustrates, smaller MUs feature small LMN cell bodies within the spinal cord and relatively few, smaller fibers, while the largest MUs feature very large LMN cell bodies and many large fibers (Mendell, 2005). This type of organization influences force production because the amount of contractile force generated by a MU is determined by the total volume of contractile tissue involved, as well as the preferred source of metabolism and ATPase activity (MacIntosh et al., 2006). In a small motor unit, a relatively small force can be generated because there are relatively few small, oxidative, slow-twitch fibers which presents a small volume of contractile tissue with slower cross-bridge cycling (MacIntosh et al., 2006). When a large MU is recruited, numerous large, glycolytic fast-twitch fibers present a larger volume of contractile tissue with faster cross-bridge cycling to produce much a greater force.

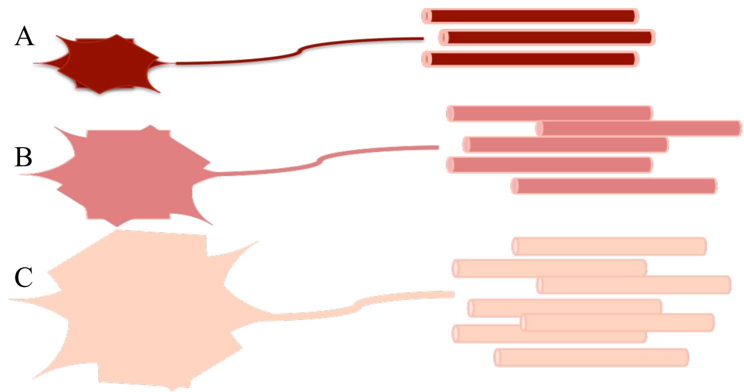

Figure 3. Schematic illustrations of A; small, B; medium and C; large motor units. Cell body and number of fibers increasing with size

Further, motor units are not uniformly distributed by size throughout every muscle belly. In general, large muscles used for gross movements like the deltoid, biceps or quadriceps favor larger MUs, while muscles used for fine movement like speech often have more small MUs to allow for finely coordinated movements (MacIntosh et al., 2006). Thus, in most large skeletal muscles of the upper and lower extremities, much of the cross-sectional area is comprised of fibers belonging to large MUs (MacIntosh et al., 2006) (see figure 4). Unfortunately in the case of ALS, there is preferential targeting of the largest motor units early in the disease (Fischer et al., 2004), the loss of

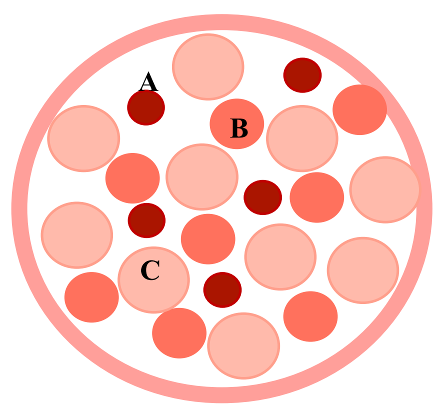

Figure 4. Schematic cross-section of a bicep muscle belly. A: fibers from small MUs B: fast-oxidative fibers from medium Mus, C: fast-glycolytic fibers of large MUs

large MUs severely impacts both force production and muscle size early in the disease and manifests clinically as weakness and wasting.

Once compromised by the disease, it appears that motor units may degenerate in a retrograde fashion (Fischer et al., 2004). The cell body, axon and neuromuscular junction (NMJ) were examined at multiple time points in an animal model of ALS and revealed that denervation is first observed at the NMJ, followed by a period of motor axon loss before loss of motor neuron cell bodies (Fischer et al., 2004). Similarly, in a human case report of an individual with a 6-month history of sporadic ALS who passed away from unrelated causes, post-mortem autopsy revealed denervation and reinnervation changes in muscle but the motor neurons remained normal (Fischer et al., 2004). In both the rodent model and human case study, evidence of disease (i.e. muscle denervation) was observed at the level of the muscle before it was detected at the level of the motor neuron in the spinal cord or brain. Collectively, these observations suggest that in ALS, denervation may begin at the distal axon in a "dying back" pattern.

In a clinical setting, evidence of disease-related denervation is investigated using peripheral nerve conduction studies (NCS) and needle electromyography (EMG). NCS allows the clinician to locate nerve involvement and exclude other treatable neuropathies (e.g. chronic inflammatory demyelinating polyneuropathy). Motor NCS in ALS typically feature asymmetric side-to-side differences, decreased amplitude, prolonged distal motor latency, and slower conduction velocity consistent with axon loss (Joyce & Carter, 2013), all of which point to disease-related degeneration of specific nerves.

While NCS help to identify nerve involvement, needle EMG is used to detect acute and chronic denervation at the muscle. A major feature of active denervation is the spontaneous contraction of individual muscle fibers, called fibrillation potentials (Daube & Rubin, 2009). These small twitches happen at rest and are undetectable to the eye but easily identified by needle EMG. When muscle fibers lose their parent axon, the acetylcholine receptors typically confined to the motor end plate begin to spread diffusely across the muscle membrane and this increased exposure can lead to spontaneous depolarizations (Ko, Anderson, & Cohen, 1977). Fibrillations indicate active denervation because they appear immediately following retraction of the neuromuscular junction.

In addition to fibrillations, another sign of denervation detected by needle EMG is the positive sharp wave. Damaged ion channels of a denervated muscle fiber are unable to open quickly enough to conduct an action potential down the fiber; on an EMG recording this appears as a brief positive potential that slowly decays (Daube & Rubin, 2009) and indicates active denervation. The last form of spontaneous activity common to ALS is the fasciculation; depolarization of an entire motor unit causing a visible muscle twitch. This spontaneous motor unit action potential can be generated anywhere along the LMN, from the anterior horn cell to the nerve terminal, though most commonly from spontaneous firing at the nerve terminal (Daube & Rubin, 2009). Fasciculations can happen in healthy people but in ALS muscle twitches occur in the context of weakness and signify neurodegeneration (Ludolph et al., 2015). Patients with ALS may experience very large fasciculations which result from depolarized motor units that have adopted orphaned muscles fibers through collateral reinnervation (MacIntosh et al., 2006). As discussed above, when a muscle fiber loses its parent neuron it will atrophy and release a combination of chemical signals as a "call out for help" (see figure 5, early denervation). Occasionally these calls are met by a neighbouring motor neuron that will sprout a

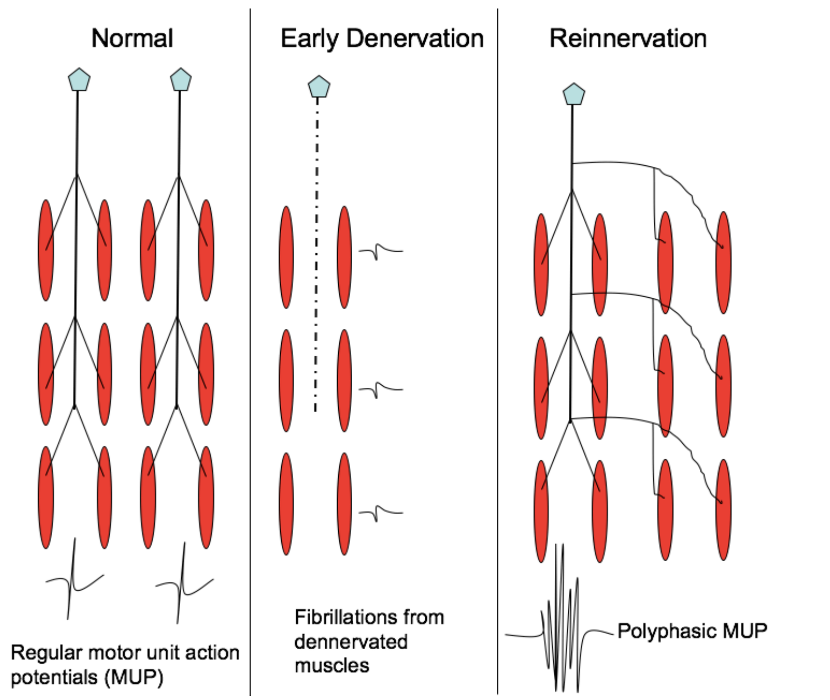

Figure 5. Schematic illustrating motor unit action potential (MUP) under normal conditions, spontaneous activity of fibrillations during early denervation and a polyphasic MUP resulting from collateral reinnervation. (Taylor, 2016)

new axon to adopt the orphaned fiber into its own motor unit (MacIntosh et al., 2006). On an EMG recording this motor unit will feature a larger amplitude, longer duration and poly-phasic action potential as it struggles to coordinate the activity of its many muscle fibers (Daube & Rubin, 2009) (see figure 5). While these features enable very easy detection of chronic denervation using EMG, collateral reinnervation can diminish the effects of denervation on wasting and weakness (MacIntosh et al., 2006) which in some cases can prolong the time from disease onset to symptom recognition and subsequent clinical investigation.

In summary, ALS is a neurodegenerative disorder that causes selective death of motor neurons leading to skeletal muscle atrophy and paralysis. The largest motor units are preferentially targeted and lost early in the disease which explains clinical symptoms of weakness and wasting. Sometimes orphaned muscles fibers are reinnervated by neighbouring motor units and this process, in addition to other features of acute and chronic denervation, are detected clinically using nerve conduction studies and electromyography. The neurodegenerative features of ALS are well-defined and allow clinicians to reach the diagnosis after ruling out all other possible causes (Ludolph et al., 2015).

2.3 Mechanisms of Disease

Though relatively little is known about the mechanisms of action, several genes and features of pathology have been identified in animal and human cases of ALS. In patients diagnosed with sporadic and familial ALS, ubiquitinated aggregates are present in the spinal cord at the time of autopsy (Piao et al., 2006). The term ubiquitinated aggregate refers to an abnormal accumulation of intermediate filaments, misfolded proteins or neurofilaments in the cell body and axon that are tagged with ubiquitin for disposal (Boillée, Vande Velde, & Cleveland, 2006). While their presence is widely recognized, the precise source of aggregate production is not entirely clear.

In ALS, one of the most important intraneuronal protein aggregates is TDP-43 (43kDa TAR DNA-binding protein) found in most sporadic and familial forms, except for a small number caused by a mutation of SOD1 (superoxide dismutase) or FUS RNA binding protein (FUS) (Lagier-Tourenne & Cleveland, 2009). Unfortunately, it is not known whether TDP-43 aggregation is a primary event in ALS pathogenesis or a by-product of the disease (Lagier-Tourenne & Cleveland, 2009). The normal and mutant roles of TDP-43 are under investigation to better elucidate its link to ALS pathogenesis. Available evidence suggests a role for pathologic TDP-43 in transcription, RNA splicing, transport and even translation (Lagier-Tourenne & Cleveland, 2009; Neumann et al., 2009).

Prior to the discovery of TDP-43, the majority of mechanistic research efforts focused on SOD1 a mutation linked to 20% of familial ALS (Rosen et al., 1993). In this form of familial ALS, protein aggregates have been found to localize to the mitochondria (Boillée et al., 2006) where they interfere with the ability to transport mitochondrial protein synthesized in the cytosol to the mitochondria by blocking specialized transporters on the membrane (Liu et al., 2004) thus contributing to mitochondrial dysfunction. This is particularly problematic because mitochondrial dysfunction is tightly linked to oxidative stress (Nicolson, 2014). Mitochondria are the main source of reactive oxygen species (ROS), highly reactive free radicals produced by the electron transport chain as a by-product of oxidative phosphorylation (Nicolson, 2014) and when dismutase enzymes and antioxidants are unable to adequately neutralize ROS, free radicals can damage cellular lipids, proteins and DNA; this is referred to as oxidative damage (Nicolson, 2014). Detrimental to neuronal function, oxidative damage is recognized as a common feature of neurodegeneration for many forms of ALS (Boillée et al., 2006). Again, in the case of the SOD1 animal model, pathologic superoxide dismutase (an abundant cytosolic enzyme) unable to detoxify as normal (Boillée et al., 2006) enhances neuron vulnerability to oxidative damage.

Importantly, cell types beyond the motor neuron like the neighbouring astrocyte and microglia have also been implicated in the disease. Under healthy conditions the microglia function as the main form of defence for the CNS by working like scavengers to remove foreign substances and any other threats to neuronal health (Lull & Block, 2010). In response to CNS damage or disease, activated microglia can release cytotoxic factors like nitric oxide and ROS aimed at destroying invaders (Lull &

Block, 2010) however this increased production of ROS can enhance oxidative stress for a vulnerable, pathologic motor neuron. In this way, the support cell can contribute to more harm than help, and ultimately accelerate disease progression (Boillée et al., 2006).

Similarly, the astrocyte normally supports motor neuron health by providing trophic factors (molecules that support neuron growth) and removing synaptic glutamate (Boillée et al., 2006). As discussed in section 2.2, glutamate is the neurotransmitter involved in the synapse between upper and lower motor neurons. If present in excess such as with repetitive firing, glutamate can induce excitotoxicity which is highly damaging to the neuron (MacIntosh et al., 2006). For this reason, the role of astrocytes in mediating rapid recovery of glutamate is tremendously important. Unsurprisingly, diminished glutamate transport has been implicated in ALS (Fray et al., 1998; Maragakis, Dykes-Hoberg, & Rothstein, 2004; Rothstein, Martin, & Kuncl, 1992) and glutamate-induced excitotoxicity remains a prominent therapeutic target.

In summary, several genetic mutations have been linked to forms of ALS of which SOD1 and TDP-43 have garnered most attention. While the exact, specific mechanisms underlying ALS are unclear, ubiquitinated aggregates, mitochondrial dysfunction, oxidative damage and glutamate-induced excitotoxicity are some of the major pathological features of ALS.

2.4 Clinical Phenotypes and Functional Decline

There are a variety of clinical phenotypes for ALS determined by body region of onset, degree of involvement for UMN and LMN, and rate of progression (J. M. Ravits & La Spada, 2009). Three major body regions are traditionally used to classify disease onset; limb (70%), bulbar (25%) and respiratory (5%) (Chio et al., 2013) though individual patients present varied phenotypes within each class. For example, someone presenting with initial symptoms in the hand and someone with deficits in the leg are both classed as limb-onset. The signs and symptoms of interest arise from disturbance to UMN and LMN, both of which must be present and unexplained by other causes to be diagnosed with ALS (for details outlining the complete diagnostic criteria please refer to the World Federation of Neurology Consensus Guidelines for Diagnosis; Brooks, Miller, Swash, & Munsat, 2000). Muscle weakness, spasticity, hyperreflexia and pathological reflexes (e.g., a positive Babinski response) all indicate UMN disturbance, while LMN deficits manifest as muscle wasting (figure 6), further weakness and fasciculations (Ferguson, 2007).

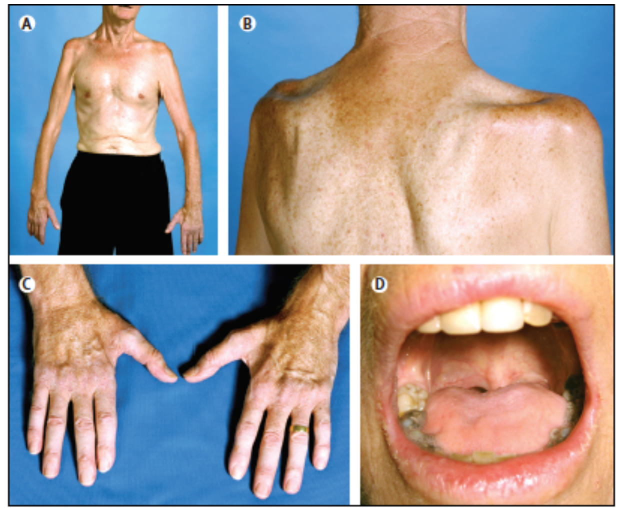

Figure 6. Muscle atrophy consistent with ALS A: deltoid wasting B: Loss of supraspinatus, infraspinatus and deltoid C: Wasting of the thenar muscles between the thumb and first finger D: wasting of the tongue, difficulty with mouth-opening (Kiernan et al., 2011)

A patient with limb onset might present with muscle weakness and wasting of the shoulder and hands (figure 6A and C) paired with fasciculations and disturbed reflexes, but with well-preserved muscles for speech and swallowing (Kiernan et al., 2011). Conversely, a patient with bulbar onset might be visibly unaffected in the limbs but present with difficulty opening their mouth fully, atrophy of the tongue (figure 6D), a change in voice quality and fasciculations of the tongue and face. The anatomical site of onset and mix of UMN/LMN signs creates a range of clinical phenotypes at the onset of ALS.

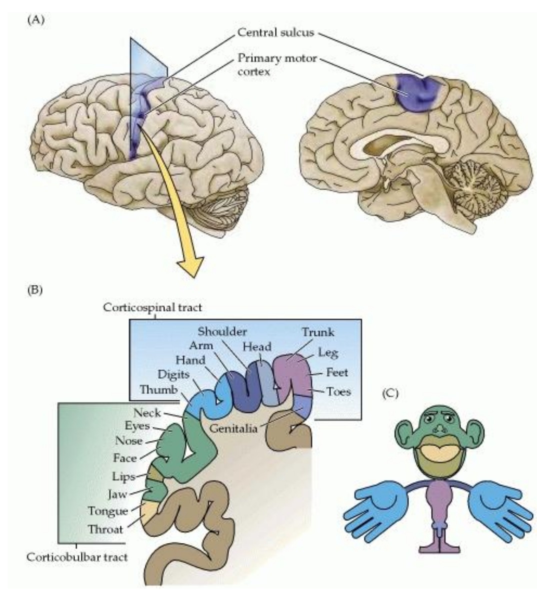

Figure 7. Depicting the somatotopic organization of the spinal motor neurons (Purves et al., 2001)

Over the course of the disease symptoms appear to spread to contiguous anatomic regions over time (J. M. Ravits & La Spada, 2009). This relatively orderly pattern of degeneration is attributed to the somatotopic organization of the CNS; the arrangement of motor neurons within the primary motor cortex and spinal cord mirrors the organization of anatomic body (see figures 7 and 8) and as the disease affects the next closest pool of motor neurons in the brain or spinal cord, the clinical symptomology will typically present in an adjacent anatomic region (J. Ravits et al., 2007). Granted this pattern of disease spread is complicated by concurrent degeneration in two separate 3-dimensional motor neuron pools (the motor cortex and spinal cord), and due to differences in individual neuroanatomy even two patients with the same discrete site of onset could develop symptoms in different areas at different times (J. M. Ravits & La Spada, 2009). Disease progression is undoubtedly complex and the clinical presentation can vary greatly between individuals.

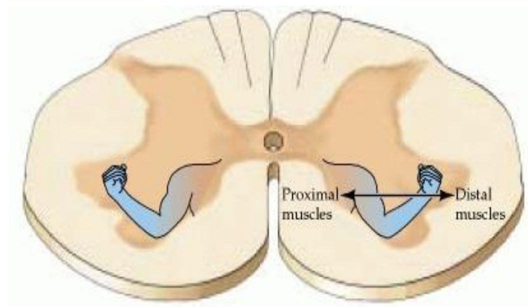

Figure 8. Depicting the somatotopic organization of the motor cortex (Purves et al., 2001)

In general, certain phenotypes of symptom onset are associated with more favourable prognosis than others. Limb-onset, younger age of onset and diagnostic delay (longer time taken to arrive at the diagnosis) are independently associated with prolonged survival while initial bulbar and respiratory weakness, and older age of onset are associated with shorter survival (Talbot, 2009). Of course, there are both slow and rapid progressors within each of these classes with no known reasons for this underlying variance (Talbot, 2009). Progression rates may reflect differences in the relative potency for an underlying pathogenic factor, or differences in disease-modifying genes that may accelerate or slow the pathogenesis (J. M. Ravits & La Spada, 2009). Unfortunately, the inherent heterogeneity of clinical phenotypes and progression rates pose challenges to research efforts seeking to better understand the physiological changes underlying disease progression.

From a clinical standpoint, disease progression is marked by functional decline and changes in the ability to perform activities of daily living. The revised ALS Functional Rating Scale (ALSFRS-R) (appendix D) is a 12-item questionnaire often used to quantify functional change in patients with ALS (Franchignoni et al., 2013) by quantifying the ease of movement across several domains including speech, dressing, climbing stairs and breathing. Scores for each item range between 4 (normal function) and 0 (loss of function), amounting to total scores between 48 and 0. The average patient with ALS loses 0.9

ALSFRS-R points per month (Castrillo-Viguera et al., 2010), though there is considerable variability in the rate of decline between individual patients. Given that there is presently no cure for ALS, treatment strategies are largely aimed at preserving quality of life and adapting to changes in functional decline.

2.5 Current Treatment and Therapeutic Strategies

Given the complexity and uncertainty regarding the pathophysiology of ALS, treatment options remain extremely limited in number and effectiveness. Until very recently, the pharmaceutical riluzole has been the only Food and Drug Administration (FDA) and Health Canada approved medication for ALS treatment. This orally administered drug inhibits glutamate release with the intentions of minimizing cellular disruptions caused by glutamate excitotoxicity (described in section 2.2). In two large randomized controlled trials, riluzole extended survival by 3-6 months (Bensimon, Lacomlez, & Meininger, 1994; Lacomlez, Bensimon, Leigh, Guillet, & Meininger, 1996), and most beneficial effects were seen in patients with moderate functional impairment.

On May 5th 2017 a new drug, Edaravone gained FDA approval for ALS treatment in the United States and will be marketed as Radicava. Edaravone is a free-radical scavenger that helps to protect neurons from oxidative damage, a feature of pathology outlined in section 2.2 (Shichinohe et al., 2004). Edaravone is delivered via intravenous infusion 10-14 days at a time followed by a drug holiday of similar length and has been shown to modestly slow decline of physical function compared with placebo (Abe et al., 2014), it is not yet known whether the drug influences survival. Nearly four times the price of the drug in Japan, edaravone will cost $145, 524 USD per year and has not yet been approved for use in Canada (Herper, 2017).

With few pharmaceutical options, the management of ALS is comprised largely of treatments aimed at improving quality of life by reducing the severity of symptoms, rather than disease progression itself (Kiernan et al., 2011). This approach to symptom management typically involves a multidisciplinary team including neurology, physiatry, respirology, palliative care, dietetics, occupational therapy, physiotherapy and social work. Specialists often prescribe medications to reduce muscle cramps, spasticity, excessive salivation and fatigue while dietary interventions are used to maintain body weight. Non-invasive assistive ventilation like the BiPAP (bilevel positive airway pressure) machine is commonly used to support breathing as needed and adaptive devices for speech, coughing, dressing and general mobility can be provided to support independence and autonomy during activities of daily living (Kiernan et al., 2011). Over time patients require increasing support with all activities of daily living. Social workers support this transition by arranging home-care from personal support workers and nursing staff to reduce the direct responsibilities of friends and family members susceptible to caregiver burnout.

In addition to the provision of adaptive resources, patients with ALS can benefit from physical therapy to maintain mobility and minimize the development of complications (Lewis & Rushanan, 2007). However, healthcare professionals have been historically hesitant to prescribe exercise because of concerns related to the debunked burn-out hypothesis whereby exercise training was thought to "burn out" remaining motor units in ALS and thus increase the rate of disease progression (Chen, Montes, & Mitsumoto, 2008). Unfortunately, the relative dearth of evidence in humans does little to encourage many clinicians to prescribe exercise for patients as a means of preventing further deconditioning and prolonging functional independence (Dal Bello-haas, Florence, & Krivickas, 2008).

2.6 Exercise and ALS

Moderate intensity aerobic exercise may be useful to slow endurance deficits, degeneration of skeletal muscle and the loss of motor neurons in ALS (Dal Bello-Haas et al., 2007; Drory et al., 2001; Lui & Byl, 2009; Pinto et al., 1999). While specific physiological mechanisms in humans remain unclear, studies using animal models have suggested that aerobic exercise could reduce neuronal inflammation, increase cellular energy levels and help remove damaged intracellular proteins (De Almeida et al., 2012; Deforges et al., 2009; Kaspar et al., 2005; Kirkinezos & Hernandez, 2003).

As well, moderate aerobic exercise may increase levels of neurotrophins (Gold et al., 2003), a type of chemical compound that supports the growth, function and survival of neurons (Henriques, Pitzer,

& Schneider, 2010). Several neurotrophins including brain derived neurotrophic factor (BDNF), glial derived neurotrophic factor (GDNF), insulin-like growth factor (IGF-1) and vascular endothelial growth factor (VEGF) have been found to increase with exercise (Carro et al., 2000; Carro et al., 2001; Nave, 2010; Neeper et al., 1995) and thus have been subject to much interest for their neuroprotective, therapeutic potential in ALS treatment. Unfortunately, exogenous supplementation of these neurotrophins has been unsuccessful in all trials to date but hope remains that endogenous production of neurotrophins up-regulated by exercise may present a useful therapeutic target (Henriques et al., 2010).

2.6.1 Exercise Therapy and Animal Models of ALS

Several investigations have assessed the effects of aerobic exercise training on animal models of ALS (summary presented in table 2.1). One study exercised mice for 30 minutes per day, 5 days per week and found an increased life expectancy and delayed loss of spinal motor neurons compared to controls (Kirkenzos & Hernandez, 2003). Liebetanz and colleagues (2004) investigated a much larger volume of exercise (10 hours per day, 5 days per week) finding no adverse outcomes and increased life spans in the exercised rodents versus controls. Another study concluded that mice engaged in continuous aerobic exercise training had significantly improved motor performance, higher density of motor neurons in the spinal cord and slowed onset of muscle weakness compared to the sedentary rodents (Carreras et al., 2010). Further studies point to other mechanisms including decreased levels of neuroinflammatory molecules in the spinal cord, increased levels of oligodendrocytes (Deforges et al., 2009) and increased intracellular clean-up of harmful proteins (Itoh et al., 1998) that may contribute to prolonged motor function and survival with exercise.

While evidence for exercise in animals with ALS is encouraging, there are considerable limitations to using rodent models to study the disease. Primarily, the bulk of exercise research has employed the mutant SOD1 rodent model developed in 1994 by Gurney and colleagues following the discovery linking the SOD1 gene and familial forms of ALS (Rosen et al., 1993). While this model does strongly resemble many features of some familial forms of ALS (Gurney et al., 1994), these amount to less than 2% of all human cases. Further, the SOD1 rodent model does not feature TDP-43 inclusions in the central nervous system, a hallmark characteristic of nearly every other form of sporadic and familial ALS (Boillée et al., 2006). Thus, the rodents used may represent an entirely different underlying pathology which poses serious limits to whether physiological effects of exercise found in the animal studies are applicable to exercise in most forms of human ALS.

Table 2.1 Exercise and ALS trials in animal models

Study	Description of Exercise	Effect on Motor Performance	Effect on Survival Time
Kirkinezos et al 2003	Motorized treadmill, mice run 13 m/min for 30 min 5 days/week (n = 60)	Not assessed	Exercise extended survival by 6.2% compared with sedentary controls
Mahoney et al 2004	High intensity aerobic exercise, motorized treadmill running, progressive, 9-22 min, 4-5 days/week (n = 39)	Exercise training decreased motor performance (rotarod test) earlier than sedentary	Exercise training decreased survival time in male, but not female mice, compared to controls
Liebetanz et al 2004	Motorized running wheel, 3.4 m/min for 400 min/day (n = 37)	No significant differences across grip strength, stride length or tight rope test	Exercise extended survival by 3.5% compared with sedentary controls
Kaspar et al 2005	Self-paced wheel running with varied exposure to wheel (0, 2, 6, or 12 hours/day; n = 72)	Exercise training (for 6 or 12 hrs) associated with delayed loss of motor function (rotarod) vs sedentary or low exercise volume	Self-paced exercise associated with longer survival: 5.0% (2 hrs exercise group), 28.0% (6 hrs) and 18.0% (12 hrs)
Carreras et al 2010	Treadmill running; high intensity (60 min/day, 5 day/week at 20 m/min) and moderate intensity (30 min/day; 3 days/week at 19 m/min; n = 90)	Moderate exercise delayed motor performance decline (rotarod) and loss of lumbar motor neurons	Not assessed

2.6.2 Exercise Therapy in Human Patients with ALS

Very few studies have investigated exercise training for humans living with ALS (summary presented in table 2.2). The primary outcomes evaluated in exercise studies for human ALS include global function via ALSFRS-R, fatigue via Fatigue Severity Scale, quality of life (QoL) via Short Form-36 and muscle strength via maximal voluntary isometric contraction.

In 2001, Drory and colleagues conducted a 12-month randomized controlled trial (RCT) investigating the effect of a 15-minute twice daily home based exercise regimen on muscle strength, global function, fatigue, musculoskeletal pain, spasticity and QoL (Drory et al., 2001). Twenty-five patients were randomized to receive a moderate daily exercise program (n=14) or not to perform any physical activity beyond their usual daily requirements (n=11). Exercise regimens were individually prescribed by a certified physiotherapist and designed to have muscles of the limbs and trunk work against moderate loads (Drory et al., 2001). At three months, exercising patients showed less deterioration on the ALSFRS and scale of muscle spasticity but not on other measures. There were no significant differences between groups at six months and too few patients remained at 9 and 12 months for statistic evaluation. The researchers concluded that moderate daily physical activity has a short-lived positive effect on disability in patients with ALS and should be recommended (Drory et al., 2001).

Over a period of six years Dal Bello-Haas and colleagues recruited 27 participants for a 6-month parallel group RCT (Dal Bello-Haas et al., 2007). Participants were randomized to a home-based exercise program consisting of daily stretching with or without moderate intensity resistance exercise three times weekly. Eight exercise and ten daily stretching only (control) participants completed the study. Global function and QoL were significantly higher in the resistance exercise group at 6 months. The exercisers also demonstrated less decline in leg strength measured by maximal voluntary isometric contraction (Dal Bello-Haas et al., 2007). As with the study above, this trial reported notable drop-out in both groups. Participants withdrew for reasons related to perceived disease progression, perceived lack of benefit from the study, depression or incompliance to the study protocol.

Recently, a research group at the NEuroMuscular Omnicomprehensive Center (NEMO) in Milan, Italy conducted a 6-month, single-blinded RCT (Lunetta et al., 2016). Lunetta and colleagues report preliminary findings from their investigation on the effects of three strictly monitored exercise programs (SMEP) and a "usual care" (UCP) home-based passive exercise program. Sixty ALS patients were randomly assigned to UCP or one of three subgroups of SMEP 1) an active resistance exercise program of the upper and lower limbs combined with cycle ergometry 2) only active resistance exercises and 3) passive exercise of 20 flexion-extension movements in the upper and lower limbs. For six consecutive months, participants were treated daily by a trained physiotherapist for two weeks each month at NEMO followed by home treatment by a trained caregiver minimizing the number of monthly visits to reduce risk of drop-out. UCP participants were treated with passive and stretching exercises at home twice weekly. Participants in all SMEP groups had significantly higher ALSFRS-R scores compared to the UCP group at the end of the treatment period and at six-month follow-up. No effects of training were found for survival, respiratory decline or QoL measured by the McGill Quality of Life questionnaire. From these preliminary results, the authors conclude that a strictly monitored exercise program may reduce motor deterioration in ALS patients (Lunetta et al., 2016).

Other studies have investigated the utility of assistive ventilation and supportive treadmill walking (Pinto et al., 1999; Sanjak et al., 2010) to improve exercise tolerance for patients experiencing respiratory and gait challenges, however no studies have explored the use of intermittent exercise like sprint interval training (SIT). This low-volume alternative to traditional long duration endurance training provides a potent stimulus for aerobic adaptation by matching short effortful intervals with periods of recovery (Gibala et al., 2006). By minimizing the respiratory limitations of long duration continuous exercise, SIT has been well tolerated in other clinical populations with reduced exercise tolerance (Moholdt et al., 2009; Warburton et al., 2005; Wisloff et al., 2007), and may be useful for people with ALS.

Additionally, studies have neglected to investigate any underlying physiological effects of exercise training and focus solely on functional outcomes. For example, these studies have not included muscle biopsies, serum levels of neurotrophins, quantitative measures of exercise capacity (i.e. VO_2 max) or magnetic resonance imaging-related measures of the central nervous system. Thus, much remains unknown about how exercise may be reducing motor deterioration in ALS patients.

It is very important to acknowledge that there are numerous challenges to conducting a large randomized controlled trial for humans with ALS including heterogeneity of disease pattern and progression rates, relatively low prevalence and incidence, limited number of large clinical centers devoted to ALS and competing recruitment for clinical trials. These factors influencing research feasibility will be further explored in section 2.7 and in Chapters 5 and 6.

Table 2.2 Exercise intervention studies in human ALS

Study	Description of Exercise	Effect on Functional Performance (ALSFRS-R)	Spasticity and Fatigue	Quality of Life (QoL)
Pinto et al 1999	Treadmill until anaerobic threshold; coupled with non-invasive assisted ventilation for 1 year (n = 20)	Lower rate of functional decline, significant over 12 months	Not assessed	Not assessed
Drory et al 2001	Moderate intensity, unsupervised; 15 min, 2x/day for 6 months (n = 25)	Lower rate of decline, significant at 3 months but not 6 months	Spasticity decreased at 3 months; trend for less fatigue-related symptoms	Trend for less decline in QoL relative to non-exercisers
Bello-Haas et al 2007	Moderate load and intensity; individualized program according to patient tolerance and limitations over 6 months (n = 27)	Lower rate of decline, significant over 6 months; slowed decline in lower extremity strength	Not assessed; no difference in respiratory function	Less decline in QoL relative to non-exercisers
Sanjak et al 2010	Weight-supported treadmill for 30 min, broken up in 5-min segments, 3 times per week for an 8-wk period (n = 6)	Improved ALSFRS-R; improved gait speed, distance walked and stride length in 6 Minute Walk Test	Not assessed	Not assessed

Lunetta et al 2016	Moderate intensity, supervised; 1) upper and lower limb active resistance exercise coupled with cycle ergometry 2) only active resistance 3) passive assisted whole body flexion-extension	Lower rate of functional decline at 6 and 12 months	Not assessed	No effect on QoL

2.7 Barriers and challenges for the use of exercise as therapy

Living with ALS introduces new barriers and challenges to engaging in exercise including exercise intervention studies. Physical symptoms related to the disease like general fatigue, weakness and spasticity can interfere with one's ability to perform exercises they once performed with ease. Respiratory weakness can also impair exercise tolerance (Mezzani et al., 2012) and contribute to general fatigue (Sharma et al., 1995). Feeling acutely uncomfortable during exercise may deter individual participation.

Like persons with developmental or acquired physical disabilities, people living with ALS also contend with environmental barriers to accessing appropriate exercise programs. Identifying barriers and facilitators to exercise is particularly important because the number of self-perceived barriers to physical activity (PA) is a key predictor of exercise participation (Phillips, Flemming, & Tsintzas, 2009). A study examining self-perceived barriers to exercise found that patients with ALS cite a greater number of obstacles than healthy controls, including; including lack of energy, feeling self-conscious, "health concerns" and difficulty engaging in PA (Phillips et al., 2009). Another study found that for individuals with neurological conditions including ALS, the most common barriers to exercise were embarrassment, perceived lack of condition-specific knowledge of fitness professionals about neurological disease and the impact of that on exercise advice (Elsworth et al., 2009). Fortunately, these findings present some targets that can be addressed to better facilitate exercise therapy and exercise intervention research in this population. However, it is very important to recognize that physical, environmental and psychological barriers intersect uniquely for each person. Further research is required to explore how the experience of living with ALS and other neuromuscular disorders impacts attitudes towards exercise and whether perceived benefits of exercise are different throughout the disease process.

2.8 Thesis Hypotheses

Broadly stated, the primary purpose of this thesis was to examine the role of exercise for people living with ALS. The objective of Chapter 3 was to a) compare the acute tolerance of traditional endurance training and sprint interval training and b) investigate the effect of a six-week sprint interval training program on aerobic fitness, global function and fatigue severity in people living with ALS. It was hypothesized that sprint interval training would be better tolerated than endurance training and that six weeks of training would improve measured outcomes. Due to unforeseen recruitment challenges, these objectives were examined in a sample of one participant. Chapter 4 outlines a fundamental reworking of the research objectives which led to the exploration of lived experience for people with ALS. The objective of Chapter 5 was to explore the subjective accounts of people with ALS to better understand how their lived experience impacts the ways they engage in physical activity and exercise. It was hypothesized that the everyday experience of living with a progressive and terminal neuromuscular disease is implicated in how someone thinks about and engages with exercise.

2.9 References

Abe, K., Itoyama, Y., Sobue, G., Tsuji, S., Aoki, M., Doyu, M., … Yoshino, H. (2014). Confirmatory double-blind, parallel-group, placebo-controlled study of efficacy and safety of edaravone (MCI-186) in amyotrophic lateral sclerosis patients. *Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration*, *15*(7–8), 610–617. https://doi.org/10.3109/21678421.2014.959024

Bensimon, G., Lacomlez, L., & Meininger, V. (1994). A controlled trial of riluzole in amyotrophic lateral sclerosis. *The New England Journal of Medicine*.

Boillée, S., Vande Velde, C., & Cleveland, D. W. (2006). ALS: A Disease of Motor Neurons and Their Nonneuronal Neighbors. *Neuron*, *52*(1), 39–59. https://doi.org/10.1016/j.neuron.2006.09.018

Brooks, B. R., Miller, R. G., Swash, M., & Munsat, T. L. (2000). El Escorial revisited: Revised criteria for the diagnosis of amyotrophic lateral sclerosis. *Amyotrophic Lateral Sclerosis and Other Motor Neuron Disorders*, *1*(5), 293–299. https://doi.org/10.1080/146608200300079536

Burke, R. E. (2011). Motor Units: Anatomy, Physiology, and Functional Organization. *Comprehensive Physiology*, (543). https://doi.org/10.1002/cphy.cp010210

Carreras, I., Yuruker, S., Aytan, N., Hossain, L., Choi, J. K., Jenkins, B. G., … Dedeoglu, A. (2010). Moderate exercise delays the motor performance decline in a transgenic model of ALS. *Brain Research*, *1313*(151), 192–201. https://doi.org/10.1016/j.brainres.2009.11.051

Carro, E., Nuñez, A., Busiguina, S., & Torres-Aleman, I. (2000). Circulating insulin-like growth factor I mediates effects of exercise on the brain. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *20*(8), 2926–2933. https://doi.org/10.1016/j.tins.2006.06.011

Carro, E., Trejo, J. L., Busiguina, S., & Torres-Aleman, I. (2001). Circulating insulin-like growth factor I mediates the protective effects of physical exercise against brain insults of different etiology and anatomy. *Journal of Neuroscience*, *21*(15), 5678–5684. https://doi.org/21/15/5678 [pii]

Castrillo-Viguera, C., Grasso, D. L., Simpson, E., Shefner, J., & Cudkowicz, M. E. (2010). Clinical significance in the change of decline in ALSFRS-R. *Amyotrophic Lateral Sclerosis*, *11*(1–2), 178–180. https://doi.org/10.3109/17482960903093710

Chen, A., Montes, J., & Mitsumoto, H. (2008). The Role of Exercise in Amyotrophic Lateral Sclerosis. *Physical Medicine and Rehabilitation Clinics of North America*, *19*(3), 545–557. https://doi.org/10.1016/j.pmr.2008.02.003

Chio, A., Logroscino, G., Traynor, B. J., Collins, J., Simeone, J. C., Goldstein, L. A., & White, L. A. (2013). Global epidemiology of amyotrophic lateral sclerosis: A systematic review of the published literature. *Neuroepidemiology*, *41*(2), 118–130. https://doi.org/10.1159/000351153

Dal Bello-Haas, V., Florence, J., Kloos, A., Scheibecker, J., Lopate, G., Hayes, S., … Mitsumoto, H. (2007). A randomized controlled trial of resistence exercise in individuals with ALS. *Neurology*, *68*, 2003–2007.

Dal Bello-haas, V., Florence, J. M., & Krivickas, L. S. (2008). Therapeutic exercise for people with amyotrophic lateral sclerosis or motor neuron disease (Review) Therapeutic exercise for people with amyotrophic lateral sclerosis or motor neuron disease, (4), 2–4. https://doi.org/10.1002/14651858.CD005229.pub2.Copyright

Daube, J. R., & Rubin, D. I. (2009). Needle electromyography. *Muscle and Nerve*, *39*(2), 244–270. https://doi.org/10.1002/mus.21180

De Almeida, J. P. L., Silvestre, R., Pinto, A. C., & De Carvalho, M. (2012). Exercise and amyotrophic lateral sclerosis. *Neurological Sciences*, *33*(1), 9–15. https://doi.org/10.1007/s10072-011-0921-9

Deforges, S., Branchu, J., Biondi, O., Grondard, C., Pariset, C., Lécolle, S., … Charbonnier, F. (2009). Motoneuron survival is promoted by specific exercise in a mouse model of amyotrophic lateral sclerosis. *The Journal of Physiology*, *587*(14), 3561–3572. https://doi.org/10.1113/jphysiol.2009.169748

Drory, V. E., Goltsman, E., Reznik, J. G., Mosek, a, & Korczyn, a D. (2001). The value of muscle exercise in patients with amyotrophic lateral sclerosis. *Journal of the Neurological Sciences*, *191*(1–2), 133–137. https://doi.org/10.1016/S0022-510X(01)00610-4

Elsworth, C., Dawes, H., Sackley, C., Soundy, A., Howells, K., Wade, D., … Izadi, H. (2009). A study of perceived facilitators to physical activity in neurological conditions. *International Journal of Therapy and Rehabilitation*, *16*(1), 17–24. https://doi.org/10.12968/ijtr.2009.16.1.37936

Ferguson, T. A. and L. B. E. (2007). Clinical features and diagnosis of amyotrophic lateral sclerosis. *Continuum (Minneapolis, Minn.)*, *8*(4), 9–31.

Fischer, L. R., Culver, D. G., Tennant, P., Davis, A. A., Wang, M., Castellano-Sanchez, A., … Glass, J. D. (2004). Amyotrophic lateral sclerosis is a distal axonopathy: Evidence in mice and man. *Experimental Neurology*, *185*(2), 232–240. https://doi.org/10.1016/j.expneurol.2003.10.004

Franchignoni, F., Mora, G., Giordano, A., Volanti, P., & Chiò, A. (2013). Evidence of multidimensionality in the ALSFRS-R Scale: a critical appraisal on its measurement properties using Rasch analysis. *Journal of Neurology, Neurosurgery & Psychiatry*, *84*(12), 1340–1345. https://doi.org/10.1136/jnnp-2012-304701

Fray, A. E., Ince, P. G., Banner, S. J., Milton, I. D., Usher, P. A., Cookson, M. R., & Shaw, P. J. (1998). The expression of the glial glutamate transporter protein EAAT2 in motor neuron disease: an immunohistochemical study. *European Journal of Neuroscience*, *10*(8), 2481–2489. https://doi.org/10.1046/j.1460-9568.1998.00273.x

Gibala, M. J., Little, J. P., van Essen, M., Wilkin, G. P., Burgomaster, K. a, Safdar, A., … Tarnopolsky, M. a. (2006). Short-term sprint interval versus traditional endurance training: similar initial adaptations in human skeletal muscle and exercise performance. *The Journal of Physiology*, *575*(Pt 3), 901–911.

Gold, S. M., Schulz, K. H., Hartmann, S., Mladek, M., Lang, U. E., Hellweg, R., … Heesen, C. (2003). Basal serum levels and reactivity of nerve growth factor and brain-derived neurotrophic factor to standardized acute exercise in multiple sclerosis and controls. *Journal of Neuroimmunology*, *138*(1–2), 99–105. https://doi.org/10.1016/S0165-5728(03)00121-8

Gubbay, S. S., Kahana, E., Zilber, N., Cooper, G., Pintov, S., & Leibowitz, Y. (1985). Amyotrophic lateral sclerosis. A study of its presentation and prognosis. *Journal of Neurology*, *232*(5), 295–300. https://doi.org/10.1007/BF00313868

Gurney, M. E., Pu, H., Chiu, A. Y., Canto, M. C. D., Polchow, C. Y., Alexander, D. D., … Siddique, T. (1994). Motor Neuron Degeneration in Mice That Express a Human Cu , Zn Superoxide Dismutase Mutation. *Science*, *264*(18).

Henriques, A., Pitzer, C., & Schneider, A. (2010). Neurotrophic growth factors for the treatment of amyotrophic lateral sclerosis: Where do we stand? *Frontiers in Neuroscience*, *4*(JUN), 1–14. https://doi.org/10.3389/fnins.2010.00032

Herper, M. (2017, May 5). The first ALS drug in 22 years is approved and it costs 4 times what it does in Japan. *Forbes*.

Itoh, H., Ohkuwa, T., Yamamoto, T., Sato, Y., Miyamura, M., & Naoi, M. (1998). Effects of endurance physical training on hydroxyl radical generation in rat tissues. *Life Sciences*, *63*(21), 1921–1929. https://doi.org/10.1016/S0024-3205(98)00468-8

Joyce, N. C., & Carter, G. T. (2013). Electrodiagnosis in persons with amyotrophic lateral sclerosis. *PM and R*, *5*(5 SUPPL.), 1–15. https://doi.org/10.1016/j.pmrj.2013.03.020

Kaspar, B. K., Frost, L. M., Christian, L., Umapathi, P., & Gage, F. H. (2005). Synergy of insulin-like growth factor-1 and exercise in amyotrophic lateral sclerosis. *Annals of Neurology*, *57*(5), 649–655. https://doi.org/10.1002/ana.20451

Kiernan, M. C., Vucic, S., Cheah, B. C., Turner, M. R., Eisen, A., Hardiman, O., … Zoing, M. C. (2011). Amyotrophic lateral sclerosis. *The Lancet*, *377*(9769), 942–955. https://doi.org/10.1016/S0140-6736(10)61156-7

Kirkinezos, I. G., & Hernandez, D. (2003). Regular Exercise is Beneficial to a Mouse Model of Amyotrophic Lateral Sclerosis, 804–807.

Ko, P. K., Anderson, M. J., & Cohen, M. W. (1977). Denervated skeletal muscle fibers develop discrete patches of high acetylcholine receptor density. *Science (New York, N.Y.)*, *196*(4289), 540–542. https://doi.org/10.1126/science.850796

Lacomlez, L., Bensimon, G., Leigh, N., Guillet, P., & Meininger, V. (1996). Dose-ranging study of riluzole in amyotrophic lateral sclerosis. *The Lancet*, Dose-ranging study of riluzole in amyotrophic late.

Lagier-Tourenne, C., & Cleveland, D. W. (2009). Rethinking ALS: The FUS about TDP-43. *Cell*, *136*(6), 1001–1004. https://doi.org/10.1016/j.cell.2009.03.006

Lewis, M., & Rushanan, S. (2007). The role of physical therapy and occupational therapy in the treatment of amyotrophic lateral sclerosis. *NeuroRehabilitation*, *22*(6), 451–461.

Liebetanz, D., Hagemann, K., Von Lewinski, F., Kahler, E., & Paulus, W. (2004). Extensive exercise is not harmful in amyotrophic lateral sclerosis. *European Journal of Neuroscience*, *20*(11), 3115–3120. https://doi.org/10.1111/j.1460-9568.2004.03769.x

Liu, J., Lillo, C., Jonsson, P. A., Velde, C. Vande, Ward, C. M., Miller, T. M., … Cleveland, D. W. (2004). Toxicity of familial ALS-linked SOD1 mutants from selective recruitment to spinal mitochondria. *Neuron*, *43*(1), 5–17. https://doi.org/10.1016/j.neuron.2004.06.016

Logroscino, G., Traynor, B. J., Hardiman, O., Chiò, A., Mitchell, D., Swingler, R. J., … Beghi, E. (2010). Incidence of amyotrophic lateral sclerosis in Europe. *Journal of Neurology, Neurosurgery, and Psychiatry*, *81*(4), 385–90. https://doi.org/10.1136/jnnp.2009.183525

Ludolph, A., Drory, V., Hardiman, O., Nakano, I., Ravits, J., Robberecht, W., & Shefner, J. (2015). A revision of the El Escorial criteria - 2015. *Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration*, *16*(5–6), 291–292. https://doi.org/10.3109/21678421.2015.1049183

Lui, A. J., & Byl, N. N. (2009). A systematic review of the effect of moderate intensity exercise on function and disease progression in amyotrophic lateral sclerosis. *Journal of Neurologic Physical Therapy : JNPT*, *33*(June), 68–87. https://doi.org/10.1097/NPT.0b013e31819912d0

Lull, M. E., & Block, M. L. (2010). Microglial activation and chronic neurodegeneration. *Neurotherapeutics : The Journal of the American Society for Experimental NeuroTherapeutics*, *7*(4), 354–65. https://doi.org/10.1016/j.nurt.2010.05.014

Lunetta, C., Lizio, A., Sansone, V. A., Cellotto, N. M., Maestri, E., Bettinelli, M., … Corbo, M. (2016). Strictly monitored exercise programs reduce motor deterioration in ALS: preliminary results of a randomized controlled trial. *Journal of Neurology*, *263*(1), 52–60. https://doi.org/10.1007/s00415-015-7924-z

MacIntosh, B. R., Gardiner, P. F., & McComas, A. J. (2006). *Skeletal muscle: form and function.* (Second). Champaign, IL: Human Kinetics.

Maragakis, N. J., Dykes-Hoberg, M., & Rothstein, J. D. (2004). Altered Expression of the Glutamate Transporter EAAT2b in Neurological Disease. *Annals of Neurology*, *55*(4), 469–477. https://doi.org/10.1002/ana.20003

Mendell, L. M. (2005). The size principle: a rule describing the recruitment of motoneurons. *J Neurophysiol*, *93*(6), 3024–3026. https://doi.org/10.1152/classicessays.00025.2005

Mezzani, A., Pisano, F., Cavalli, A., Tommasi, M. A., Corrà, U., Colombo, S., … Giannuzzi, P. (2012). Reduced exercise capacity in early-stage amyotrophic lateral sclerosis: Role of skeletal muscle. *Amyotrophic Lateral Sclerosis*, *13*(1), 87–94. https://doi.org/10.3109/17482968.2011.601463

Moholdt, T. T., Amundsen, B. H., Rustad, L. A., Wahba, A., L??v??, K. T., Gullikstad, L. R., … Sl??rdahl, S. A. (2009). Aerobic interval training versus continuous moderate exercise after coronary artery bypass surgery: A randomized study of cardiovascular effects and quality of life. *American Heart Journal*, *158*(6), 1031–1037. https://doi.org/10.1016/j.ahj.2009.10.003

Nave, K.-A. (2010). Myelination and the trophic support of long axons. *Nature Reviews Neuroscience*, *11*(4), 275–283. https://doi.org/10.1038/nrn2797

Neeper, S. ., Gomez-Pinilla, F., Choi, J., & Cotman, C. (1995). Exercise and brain neurotrophins. *Nature*, 551–557. https://doi.org/10.1111/j.1365-2990.2010.01093.x

Neumann, M., Kwong, L. K., Lee, E. B., Kremmer, E., Flatley, A., Xu, Y., … Lee, V. M. Y. (2009). Phosphorylation of S409/410 of TDP-43 is a consistent feature in all sporadic and familial forms of TDP-43 proteinopathies. *Acta Neuropathologica*, *117*(2), 137–149. https://doi.org/10.1007/s00401-008-0477-9

Nicolson, G. L. (2014). Mitochondrial Dysfunction and Chronic Disease: Treatment With Natural Supplements. *Integrative Medicine (Encinitas, Calif.)*, *13*(4), 35–43. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/26770107%5Cnhttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC4566449

Pasinelli, P., & H. Brown, R. (2016). Molecular biology of amyotrophic lateral sclerosis: insights from genetics. *Nature Publishing Group*, *7*(September), 710–723. https://doi.org/10.1038/nrn1971

Phillips, M., Flemming, N., & Tsintzas, K. (2009). An exploratory study of physical activity and perceived barriers to exercise in ambulant people with neuromuscular disease compared with unaffected controls. *Clinical Rehabilitation*, *23*(8), 746–755. https://doi.org/10.1177/0269215509334838

Piao, Y.-S., Wakabayashi, K., Kakita, A., Yamada, M., Hayashi, S., Morita, T., … Takahashi, H. (2006). Neuropathology with Clinical Correlations of Sporadic Amyotrophic Lateral Sclerosis: 102 Autopsy Cases Examined Between 1962 and 2000. *Brain Pathology*, *13*(1), 10–22. https://doi.org/10.1111/j.1750-3639.2003.tb00002.x

Pinto, A. C., Alves, M., Nogueira, A., Evangelista, T., Carvalho, J., Coelho, A., … Sales-Luís, M. L. (1999). Can amyotrophic lateral sclerosis patients with respiratory insufficiency exercise? *Journal of the Neurological Sciences*, *169*(1–2), 69–75. https://doi.org/10.1016/S0022-510X(99)00218-X

Purves, D., Augustine, G. J., Fitzpatrick, D., Katz, L. C., LaMantia, A. S., McNamara, J. O., & Williams, S. M. (2001). *Neuroscience*. Sunderland, MA: Sinauer Associates.

Ravits, J., Laurie, P., Fan, Y., & Moore, D. H. (2007). Implications of ALS focality Rostral – caudal distribution of lower motor neuron loss postmortem. *Neurology*, *68*(19), 1576–1582.

Ravits, J. M., & La Spada, A. R. (2009). ALS motor phenotype heterogeneity, focality, and spread: deconstructing motor neuron degeneration. *Neurology*, *73*(10), 805–811. https://doi.org/10.1212/WNL.0b013e3181b6bbbd

Rosen, D. R., Siddique, T., Patterson, D., Figlewicz, D. A., Sapp, P., Hentati, A., … Brown, R. H. J. (1993). Mutations in Cu / Zn superoxide dismutase gene are associated with familial amyotrophic lateral sclerosis. *Nature*, *362*, 59–62.

Rothstein, J. D., Martin, L. J., & Kuncl, R. W. (1992). Decreased glutamate transport by the brain and spinal cord in amyotrphic lateral sclerosis. *The New England Journal of Medicine*.

Sanjak, M., Bravver, E., Bockenek, W. L., Norton, H. J., & Brooks, B. R. (2010). Supported treadmill ambulation for amyotrophic lateral sclerosis: A pilot study. *Archives of Physical Medicine and Rehabilitation*, *91*(12), 1920–1929. https://doi.org/10.1016/j.apmr.2010.08.009

Sharma, K. R., Kent-Braun, J. a, Majumdar, S., Huang, Y., Mynhier, M., Weiner, M. W., & Miller, R. G. (1995). Physiology of fatigue in amyotrophic lateral sclerosis. *Neurology*, *45*(4), 733–740. https://doi.org/10.1212/WNL.45.4.733

Shichinohe, H., Kuroda, S., Yasuda, H., Ishikawa, T., Iwai, M., Horiuchi, M., & Iwasaki, Y. (2004). Neuroprotective effects of the free radical scavenger Edaravone (MCI-186) in mice permanent focal brain ischemia. *Brain Research*, *1029*(2), 200–206. https://doi.org/10.1016/j.brainres.2004.09.055

Swash, M., & Desai, J. (2000). Motor neuron disease: classification and nomenclature. *Amyotroph Lateral Scler Other Motor Neuron Disord*, *1*(2), 105–112. https://doi.org/10.1080/14660820050515403

Talbot, K. (2009). Motor neuron disease. *Neurology in Practice*, *9*(5), 303–309. https://doi.org/10.1136/jnnp.2009.188151

Taylor, S. (2016, March 19) *Primer on Electrodiagnostic Testing*. [Powerpoint Presentation]

Warburton, D. E. R., McKenzie, D. C., Haykowsky, M. J., Taylor, A., Shoemaker, P., Ignaszewski, A. P., & Chan, S. Y. (2005). Effectiveness of high-intensity interval training for the rehabilitation of patients with coronary artery disease. *The American Journal of Cardiology*, *95*(9), 1080–1084. https://doi.org/10.1016/j.amjcard.2004.12.063

Wisloff, U., Stoylen, A., Loennechen, J. P., Bruvold, M., Rognmo, O., Haram, P. M., … Skjaerpe, T. (2007). Superior cardiovascular effect of aerobic interval training versus moderate continuous training in heart failure patients: A randomized study. *Circulation*, *115*(24), 3086–3094. https://doi.org/10.1161/CIRCULATIONAHA.106.675041

Wolfson, C., Kilborn, S., Oskoui, M., & Genge, A. (2009). Incidence and prevalence of amyotrophic lateral sclerosis in Canada: A systematic review of the literature. *Neuroepidemiology*, *33*(2), 79–88. https://doi.org/10.1159/000222089

Chapter 3

The Effect of Modified Sprint Interval Training in ALS

3.1 Introduction

There are numerous physical, cognitive, social and psychological benefits associated with regular exercise training across healthy and clinical populations. In the general population, exercise increases muscle strength and improves cardiovascular function both of which are crucial for independent living (Cress et al., 1999). For people living with ALS, inactivity can lead to deconditioning (loss of muscle performance) and disuse weakness which can aggravate ALS-related functional decline (Lunetta et al., 2016). Regular exercise may prevent development of comorbidities associated with deconditioning and help to preserve strength and fitness, prolonging functional independence over the course of the disease (Dal Bello-haas, Florence, & Krivickas, 2008). Exercise may also provide neuroprotective benefits, given that increased levels of neurotrophins (chemical compounds supporting the growth, function and survival of neurons) have been shown to increase with exercise in healthy adults and animals (Carro, Nuñez, Busiguina, & Torres-Aleman, 2000; Carro, Trejo, Busiguina, & Torres-Aleman, 2001; Neeper, Gomez-Pinilla, Choi, & Cotman, 1995; Rasmussen et al., 2009). It is possible that increased endogenous production of neurotrophins associated with exercise could slow degeneration of motor neurons in people living with ALS (Henriques, Pitzer, & Schneider 2010).

Moderate-load resistance exercise and steady-state cycle ergometry have been found to be safe and modestly effective for slowing functional decline in ALS (Dal Bello-Haas et al., 2007; Drory, Goltsman, Reznik, Mosek, & Korczyn, 2001; Lunetta et al., 2016). However, exercise tolerance remains an issue for training compliance (Dal Bello-Haas et al., 2007; Drory et al., 2001) as people living with ALS experience reduced muscular endurance and impaired respiratory capacity which can make traditional training regimes very difficult (Sharma et al., 1995). As an alternative to endurance exercise, sprint interval training (SIT) is an effective, low-volume mode of training that has been well-tolerated in several clinical populations with reduced exercise tolerance (Moholdt et al., 2009; Warburton et al., 2005; Wisloff et al., 2007). Short effortful intervals matched by periods of recovery provide a potent stimulus for aerobic adaptation (Gibala et al., 2006) while minimizing the respiratory limitations of long duration continuous exercise. As well, an interval with an “all-out” effort may elicit greater motor unit recruitment than low or moderate-load resistance training based on a higher level of neural input (Mendell, 2005). By activating a greater number of motor units, fewer fibers are threatened by disuse weakness and more fibers may benefit from the provision of trophic factors found with motor unit activity (MacIntosh, Gardiner, & McComas, 2006).

The purpose of the current study was to 1) compare the acute exercise tolerance of traditional endurance training and sprint interval training and 2) investigate the effect of a six-week sprint interval training program on aerobic fitness, global function and fatigue severity in people living with ALS.

3.2 Methods

3.2.1 Participants

One participant successfully completed the exercise training protocol described below. The participant was diagnosed with definite ALS based on the revised El Escorial World Federation of Neurology criteria (Ludolph et al., 2015). This diagnosis was made by a neurologist with specialized training in neuromuscular medicine, within 3 months of study enrolment. The 56-year-old participant ambulated independently and did not have concomitant cardiovascular or metabolic disease, or any other orthopaedic, neurological, or neuromuscular condition. Medical clearance for maximal exercise testing was granted by the participant’s physician. The study protocol was approved by the Health Sciences Human Research Ethics Board at Queen’s University (appendices A and B).

3.2.2 Experimental Design

The study was comprised of two phases, three visits for acute exercise tolerance and fatigue, and a six-week home based stair climbing training program. During the acute phase, the participant reported to the lab once per week for three weeks for 1) a study briefing and written informed consent 2) acute endurance exercise 3) acute sprint interval exercise. Following each visit, daily activity and self-reported fatigue were recorded. For the training study, the participant performed baseline fitness testing and questionnaires, and was then asked to perform at-home sprint interval stair climbing three days per week for six weeks and return to the lab to repeat the fitness testing and questionnaires.

3.2.2.1 Phase I: Acute exercise tolerance and fatigue.

To characterize the effect of acute exercise on overall fatigue, the participant reported to the lab at the same time every 7 days for 3 weeks for separate sessions; a non-exercise control visit, a sprint interval training session and endurance training session. The participant was asked to wear an accelerometer device at the right hip during waking hours between weekly laboratory visits and record times of non-wearing (i.e. while swimming or showering) on a data tracking sheet. Self-reported fatigue was assessed at 4, 8 and 24 hours following each laboratory visit via text message which asked the participant to respond to the question, "on a scale from 0 to 10 with 0 being not fatigued at all and 10 being extremely exhausted, how fatigued do you feel?".

The non-exercise control visit consisted of a study briefing, question and answer period and informed consent followed by a laboratory tour. The sprint interval exercise visit consisted of three 1-minute efforts ascending and descending a single flight of stairs as quickly and safely possible, separated by 2 minutes of leisurely, self-paced walking on flat ground. The participant wore a Polar heart rate monitor throughout the exercise session. Number of ascended steps, heart rate (HR) and rating of perceived exertion (RPE) were recorded at the end of each sprint.

Seven days later, the endurance bout was performed on a stationary recumbent bicycle and consisted of a 5-minute warm up with minimal resistance at a self-selected cadence, 20 minutes at 65% heart rate reserve (HRR) (Karvonen & Vuorimaa, 1988) and a 5-minute cool down. The pedaling cadence was maintained between 70-80 rpm and adjustments to cycling resistance were made as needed to ensure the participant was within 5bpm of the target HR. RPE and HR were recorded every 5 minutes.

3.2.2.2 Phase II: Six-week sprint interval stair climbing

One week following the third acute exercise visit, baseline testing for the training study began. After fasting for 12 hours, the participant reported to the lab at 0800h, when waist circumference, height and weight were taken. The participant was then provided a standardized breakfast (toasted bagel [18Kcal; 1g fat, 36 g carbohydrate, 7 g protein] with 15 g of cream cheese [44Kcal; 4 g fat, 1 g carbohydrate, 1 g protein], and 170 mL of Minute Maid apple juice [80Kcal; 0g fat, 21 g carbohydrate, 0 g protein]). After resting for 30 minutes, the participant was asked to respond to the revised ALS functional rating scale (ALSFRS-R) (Franchignoni, Mora, Giordano, Volanti, & Chiò, 2013) and fatigue severity scale (FSS, appendix E) (Krupp, LaRocca, Muir-Nash, & Steinberg, 1989) used to assess global function and fatigue respectively.

The participant then performed a functional test for agility and dynamic balance called the 8-foot Up and Go (8UG) (Rolenz & Reneker, 2014). This test begins with the participant seated in a chair placed securely in front of a wall, and a mark on the floor 8 feet from the chair's front legs. The participant was asked to cross their hands over their chest and as quickly as safely possible stand up from the chair, walk around the 8-foot marker and return to their seated position. The test is scored by the total time taken to complete the task.

A modified VO_2 peak test was performed on the recumbent bike; following five minutes of loadless pedaling at 70rpm, work rate was increased by 13 watts per minute equivalent to one level on the recumbent bicycle. HR and gas exchange were collected in 10-second bins throughout the step test using

Polar HR monitors (Polar Team2 Pro, Kempele, Finland) and a metabolic cart (Moxus AEI Technologies, Pittsburgh, PA), respectively. The participant was asked to cycle until volitional exhaustion, or when they could no longer maintain a cadence >55rpm.

3.2.2.3 Home-based Training

The participant was asked to perform stair climbing SIT (three 1-minute all-out efforts, as quickly and safely as possible separated by 2-minutes rest) three times weekly for six weeks. Reminder text messages were administered twice weekly to encourage training compliance. Following the 6-week intervention period the participant returned to the lab in the fasted state to repeat each of the initial measures; waist circumference, height, weight, blood sample, ALSFRS-R, FSS, 8UG and VO_2peak.

3.3 Results

One out of fifteen patients being managed for ALS in the cachment area decided to enroll in the present study. Given N=1 it was not possible to statistically assess for any potential changes. The results to follow describe the measured outcomes.

3.3.1 Participant Characteristics

The participant was enrolled in the study eleven weeks following diagnosis and presented with mild weakness in the arms and atrophy of the thenar muscles of the hands, biceps and deltoids bilaterally. Fasciculations were observed throughout the trunk, back, abdomen, thighs and upper extremities. The participant experienced mild cramping of the hands and feet and mild hyperreflexia throughout. Nerve conduction studies and needle electromyography (EMG) provided evidence of active and chronic denervation in the cervical, thoracic and lumbar segments while magnetic resonance imaging revealed cerebellar and frontotemporal atrophy of the brain. There was evidence for a degree of frontotemporal dementia, associated with forms of familial and sporadic ALS (Lomen-Hoerth, Anderson, & Miller,

2002) which causes changes to personality and behavior as well as deficits in executive function and emotional processing (Hodges & Miller, 2001). As well, the participant reported a history of disordered sleep and became habituated to waking in the morning feeling fatigued.

Table 3.1 Participant Characteristics

Age (years)	Sex	Site of onset	Disease Duration
45-60	Male	Upper extremity	3 months from diagnosis

	Baseline	Post-training
Body weight (lbs)	197.0	199.2
VO_2 peak		
(ml/min)	2747	2617
(ml/kg-min)	30.7	29.6
ALSFRS-R	48	48
FSS	21	33
VAFS	5	8
8UG (sec)	5.05	5.20

VO_2 peak; peak oxygen uptake, ALSFRS-R; revised amyotrophic lateral sclerosis functional rating scale ranging from 0 worst to 48 normal, FSS; fatigue severity scale from 64 worst fatigue to 0 normal, VAFS; visual analogue fatigues scale from 0 worst fatigue to 10 normal, 8UG; 8 foot up-and-go timed test.

3.3.2 Acute Tolerance and Fatigue

Average heart rate throughout the SIT and endurance cycling bouts were similar and reported RPE was the same for both modalities (table 3.2). There was no difference in reported fatigue at any time point following the non-exercise, stair climbing SIT or endurance cycling visits.

Table 3.2 Acute Tolerance to Exercise Bouts

Sprint Interval Stair Climbing			Endurance Cycling 65%HRR		
	HR	RPE		HR	RPE
Warm-up	97	8	0:00	57	6
Sprint 1	141	11	5:00	98	6
Rest 1	125	8	10:00	122	11
Sprint 2	161	11	15:00	123	11
Rest 2	135	8	20:00	126	11
Sprint 3	149	11	25:00	130	9
Cool down	88	7	30:00	115	7

HRR; heart rate reserve, HR; heart rate, RPE; rating of perceived exertion

Daily activity data following acute exercise and non-exercise visits are shown in tables 3.3 and 3.4. Activity recorded during wear-time following each laboratory visit appears to be of similar distribution between sedentary, light, moderate and vigorous activity. There did not appear to be a compensatory increase in sedentary time on the days directly following laboratory visits that would indicate substantial participant fatigue.

Table 3.3 Daily activity by intensity level

Average minutes per day	Non-exercise	END	SIT
Sedentary	659.42 ± 132.7	556.5± 53.72	622.88 ± 166.06
Light	225.4 ± 117.4	206.5 ± 90.38	230.13 ± 132.69
Moderate	11.14 ± 12.64	16.5 ± 11.09	7.13 ± 7.42
Vigorous	4.00 ± 7.93	5.00 ± 10.00	2.38 ± 6.72
Very Vigorous	0.00 ± 0.00	0.75 ± 1.50	0.00 ± 0.00

Values are expressed as mean ± standard deviation minutes of daily wear-time engaged in each activity level.

Table 3.4 Percentage of daily activity by intensity level

Activity level % daily wear time	Non-exercise	END	SIT
Sedentary	73.27 ± 14.74	71.13 ± 9.52	71.94 ± 15.51
Light	25.05 ± 13.05	25.98 ± 10.62	26.90 ± 14.78
Moderate	1.24 ± 1.4	2.13 ± 1.47	0.895 ± 0.98
Vigorous	0.44 ± 0.88	0.65 ± 1.30	0.26 ± 0.75
Very Vigorous	0.00 ± 0.00	0.10 ± 0.19	0.00 ± 0.00

Values are expressed as mean ± standard deviation percentages of weekly wear-time engaged in each activity level.

3.3.3 Home-based Training

Following six weeks of unsupervised sprint interval stair climbing, there was no change in body weight, 8-foot up-and-go score, VO_2 peak or ALSFRS-R. Fatigue severity score increased from 21 to 33 while visual analogue fatigue scale decreased from 5 to 8 where 0 is worst fatigue and 10 is normal, see table 3.1.

3.4 Discussion

The current study investigated the acute tolerance and training response to sprint interval training for people living with ALS. Our results demonstrate that both sprint interval and endurance exercise appear to be well-tolerated by an individual with ALS, that functional capacity and aerobic fitness were unchanged following six weeks of home based sprint interval stepping, and that exercise intervention studies in this population are subject to substantial challenges with recruitment.

Foremost, the author wishes to acknowledge that the participant's response to acute and chronic exercise across all measures cannot be generalized beyond the level of the individual. This participant was uncharacteristically active for the ALS patient population and was enrolled in the study during the very early stages of disease onset.

3.4.1 Acute exercise tolerance

In addition to passive, active and moderate-load resistance exercise and cycle ergometry (Dal Bello-Haas et al., 2007; Lunetta et al., 2016), the present study found sprint interval stair climbing and recumbent cycling endurance exercise to be well-tolerated by an individual with ALS. Similar heart rates and RPE responses were recorded throughout and very minimal fatigue was reported following both (table 3.2). Daily physical activity levels were also maintained after all laboratory visits (table 3.3 and 3.4) which suggests that the volume and modality of the exercise protocols were well-tolerated by this participant.

Notably, the exercise protocols were selected to accommodate individuals with potentially reduced exercise tolerance to minimize barriers of enrolment. Past intervention studies reported substantial rates of drop-out related to disease progression, ability to perform the training over time (Dal

Bello-Haas et al., 2007; Drory et al., 2001) and reports of increased fatigue (Sharma et al., 1995). Our self-paced protocol was selected to encourage recruitment and minimize the risk of subject drop-out over time. While activity patterns for neuromuscular disease have not yet been collected, the enrolled participant was uncharacteristically active compared to populations with multiple sclerosis (Motl, McAuley, & Snook, 2007), spinal cord injury (Martin Ginis et al., 2010) and observationally to clinical peers with ALS seen in the same neuromuscular clinic. Based on the participant's higher level of habitual physical activity, it is possible that the exercise stimulus for both exercise bouts was very mild. This could explain the reported RPE of 'light' and ensuing fatigue of 0 and 1 for END and SIT respectively.

Moreover, this potential underestimation of physical function speaks to the large variability in presentation and progression with ALS. A protocol designed with poor exercise tolerance in mind may not have been entirely appropriately for this individual. Exercise prescription for people diagnosed with ALS likely needs to be very flexible, individualized and appropriately challenging. Previous studies employed highly individualized but relatively low intensity and low volume protocols (Dal Bello-Haas et al., 2007; Drory et al., 2001). Perhaps future research could support simple muscular strength and aerobic fitness test score cut-offs to help clinicians guide exercise prescription that better approximates exercise tolerance to ensure that patients are challenged appropriately.

3.4.2 Rating of Perceived Exertion

There are inherent limitations of self-reported measures of RPE and fatigue. A host of psychosocial motivational and emotional factors may mediate RPE (Rejeski, 1981) and self-report ratings can be influenced by self-presentation strategies (Bradley, 1978). Therefore, it remains plausible that the mild reports of exertion and fatigue were mediated by psychological strategies aiming to preserve participant ego.

Further, the instructions to climb "as quickly and safely as possible" were consistent with the stair climbing protocol employed by Allison and colleagues (2017) found to elicit an RPE of somewhat hard to hard, increasing with each interval (13±2, 15±2, 16±1 on the 20 point Borg scale) (Allison et al., 2017). However, in an older participant group with neuromuscular disease at a heightened risk of disability inducing falls (Finlayson and Peterson 2010), attention given to precise stepping may have led the participant to select a slightly lower speed and subsequent RPE. Perhaps for this individual, increasing the number of sprint intervals from 3 to 5, or lengthening each interval to 120 seconds may have elicited an RPE of greater than ‘light’. Alternatively, instructing participants to select a pace corresponding to perceived effort >15 or ‘hard’ may be more effective than to step as ‘quickly as safely possible’.

3.4.3 Six weeks of home-based training

Functionally, the participant was very similar before and after training as demonstrated by the unchanged 8UG, ALSFRS-R and VO_2 peak values. There are numerous possible interpretations of these results; 1) VO_2 was maintained as the result of improving fitness at an equal rate of decline attributed to the disease, 2) the participant was progressing relatively slowly and a six-week time frame did not provide sufficient time to observe functional improvement or decline, 3) the rate of progression was slow enough that changes were not detectable by the ALFRS-R or 8UG over six weeks and at the same time, training did not improve aerobic fitness.

In sedentary young women, six weeks of the same stair climbing protocol 3 days per week under laboratory supervision led to a 7% mean increase in VO_2peak (Allison et al. 2017). Due to substantial feasibility limitations (distance of participant commute to the laboratory, caregiver availability etc.) all training in this study was performed outside of the laboratory setting similar to previous investigations (Drory et al. 2001; Dal Bello-Haas et al. 2007; Lunetta et al. 2016). While reminder text-messages were administered to encourage at-home training compliance, it is possible that training did not occur according to the study schedule. Therefore, it could be speculated that the lack of improvement in aerobic fitness could be attributed to low training compliance. Unfortunately, it was not feasible to record accelerometry for the duration of training and this is recognized as a methodological limitation.

Over the six-week training period, fatigue severity score (a composite score of 9 likert scales ranging from 0; no fatigue to 63; disabling fatigue) increased from 21 to 33. For a clinical population with multiple sclerosis, scores of 36 or more may indicate severe fatigue or warrant further evaluation from a physician (Krupp et al., 1989). Importantly, this participant had a history of disordered sleep and reported enhanced general fatigue at the start of each day. The participant continued to report poor quality sleep at the end of the study and this may explain the increased general fatigue beyond or in addition to the training regimen.

Interestingly, the participant reported decreasing fatigue on the visual analogue fatigue scale improving from 5 to 8 out of 10 (normal) over the six weeks. These results conflict with the direction of change to the FSS score. While a comprehension error with instructions is always possible, another interpretation might suggest that the participant recognized the impact of fatigue differently when applied to discrete aspects of his daily life. The FSS asks about the impact of fatigue on twelve different domains such as interference with work, social life, duties and responsibilities. Based on these conflicting measures it is unclear as to the directional change of the participant's perceived fatigue.

3.4.4 Recruitment Limitations

The present study was extremely limited by recruitment. The investigators recognize that successful exercise intervention studies have devoted 3-5+ years for active recruitment (Dal Bello-Haas et al. 2007; Lunetta et al. 2016) and this was not feasible for the time restraints of a master's thesis project. As well, successful studies typically involved collaboration of researching health care professionals working in large, multidisciplinary centers specializing in neuromuscular disorders (Lunetta et al. 2016; Dal Bello-Haas et al. 2007). The team of investigators for the present study is comprised of one clinical neurologist, one exercise physiologist (PhD), one clinical neuromuscular physiologist (PhD) and present MD candidate, and one master's student largely without the same clinical-research infrastructure available to other groups. Additionally, the relatively low incidence and prevalence of ALS paired with the relatively small city centre in southeastern Ontario generates a limited subpopulation for recruitment.

3.4.4 Barriers to exercise for individuals with ALS

Fourteen patients undergoing treatment for ALS in Kingston declined participation to the present study. This failure to recruit sparks many questions relating to personal barriers to exercise for people living with ALS as well as the suitability of our investigation. The literature exploring this area is relatively sparse, but evidence does suggest that ambulatory individuals living with ALS report a higher number of perceived barriers to exercise compared to their healthy peers and the nature of the barriers is different (Phillips, Flemming, & Tsintzas, 2009). Rather than lack of time or job interference reported by healthy controls (Trost et al., 2002) people living with ALS cited embarrassment, lack of energy, feeling self-conscious and lacking disease-specific exercise knowledge as barriers to participation (Elsworth et al., 2009; Phillips et al., 2009). Phillips and colleagues (2009) sought to investigate barriers to engaging in leisure-time physical activity in ambulatory individuals with ALS and it is unknown as to whether non-ambulatory patients with ALS report the same primary barriers or whether these influence enrollment decisions related to exercise intervention studies. As well, research is required to better understand how the experience of living with ALS impacts ideas about the perceived benefits and usefulness of exercise.

3.5 Conclusion

The present study attempted to investigate acute tolerance to sprint interval and continuous aerobic exercise as well as the effect of a six-week sprint interval stair climbing on aerobic fitness, global function and fatigue severity for people living with ALS. Over a period of eighteen months, one participant completed the study protocol. Both sprint interval and endurance exercise were tolerated well and aerobic fitness and global function were preserved with six weeks of training. Exercise tolerance is likely highly variable between each patient with ALS and exercise prescription likely needs to be highly individualized and appropriately challenging. Most importantly, the present study revealed substantial challenges for the feasibility of intervention research in this population. Barriers to enrollment for intervention studies in ALS patients must be better understood to investigate these questions more thoroughly.

3.6 References

Allison, M. K., Baglole, J. H., Martin, B. J., MacInnis, M. J., Gurd, B. J., & Gibala, M. J. (2017). Brief Intense Stair Climbing Improves Cardiorespiratory Fitness. *Medicine and Science in Sports and Exercise*, *49*(2), 298–307. https://doi.org/10.1249/MSS.0000000000001188

Bradley, G. W. (1978). Self-serving biases in the attribution process: A reexamination of the fact or fiction question. *Journal of Personality and Social Psychology*, *36*(1), 56–71. https://doi.org/10.1037//0022-3514.36.1.56

Carro, E., Nuñez, A., Busiguina, S., & Torres-Aleman, I. (2000). Circulating insulin-like growth factor I mediates effects of exercise on the brain. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *20*(8), 2926–2933. https://doi.org/10.1016/j.tins.2006.06.011

Carro, E., Trejo, J. L., Busiguina, S., & Torres-Aleman, I. (2001). Circulating insulin-like growth factor I mediates the protective effects of physical exercise against brain insults of different etiology and anatomy. *Journal of Neuroscience*, *21*(15), 5678–5684. https://doi.org/21/15/5678 [pii]

Cress, M. E., Buchner, D. M., Questad, K. A., Esselman, P. C., DeLateur, B. J., & Schwartz, R. S. (1999). Exercise: Effects on physical functional performance in independent older adults. *The Journals of Gerontology: Medical Sciences*, *54A*(5), M242–M248.

Dal Bello-Haas, V., Florence, J., Kloos, A., Scheibecker, J., Lopate, G., Hayes, S., … Mitsumoto, H. (2007). A randomized controlled trial of resistence exercise in individuals with ALS. *Neurology*, *68*, 2003–2007.

Dal Bello-haas, V., Florence, J. M., & Krivickas, L. S. (2008). Therapeutic exercise for people with amyotrophic lateral sclerosis or motor neuron disease (Review) Therapeutic exercise for people with amyotrophic lateral sclerosis or motor neuron disease, (4), 2–4. https://doi.org/10.1002/14651858.CD005229.pub2.Copyright

Drory, V. E., Goltsman, E., Reznik, J. G., Mosek, a, & Korczyn, a D. (2001). The value of muscle exercise in patients with amyotrophic lateral sclerosis. *Journal of the Neurological Sciences*, *191*(1–2), 133–137. https://doi.org/10.1016/S0022-510X(01)00610-4

Elsworth, C., Dawes, H., Sackley, C., Soundy, A., Howells, K., Wade, D., … Izadi, H. (2009). A study of perceived facilitators to physical activity in neurological conditions. *International Journal of Therapy and Rehabilitation*, *16*(1), 17–24. https://doi.org/10.12968/ijtr.2009.16.1.37936

Franchignoni, F., Mora, G., Giordano, A., Volanti, P., & Chiò, A. (2013). Evidence of multidimensionality in the ALSFRS-R Scale: a critical appraisal on its measurement properties using Rasch analysis. *Journal of Neurology, Neurosurgery & Psychiatry*, *84*(12), 1340–1345. https://doi.org/10.1136/jnnp-2012-304701

Gibala, M. J., Little, J. P., van Essen, M., Wilkin, G. P., Burgomaster, K. a, Safdar, A., … Tarnopolsky, M. a. (2006). Short-term sprint interval versus traditional endurance training: similar initial adaptations in human skeletal muscle and exercise performance. *The Journal of Physiology*, *575*(Pt 3), 901–911.

Henriques, A., Pitzer, C., & Schneider, A. (2010). Neurotrophic growth factors for the treatment of amyotrophic lateral sclerosis: Where do we stand? *Frontiers in Neuroscience*, *4*(JUN), 1–14. https://doi.org/10.3389/fnins.2010.00032

Hodges, J. R., & Miller, B. (2001). The Classification, Genetics and Neuropathology of Frontotemporal Dementia. Introduction to the Special Topic Papers: Part I. *Neurocase*, *7*(1), 31–35. https://doi.org/10.1093/neucas/7.1.31

Karvonen, J., & Vuorimaa, T. (1988). Heart Rate and Exercise Intensity During Sports Activities: Practical Application. *Sports Medicine: An International Journal of Applied Medicine and Science in Sport and Exercise*, *5*(5), 303–311. https://doi.org/10.2165/00007256-198805050-00002

Krupp, L., LaRocca, G., Muir-Nash, J., & Steinberg, A. (1989). The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. *Arch Neurol*, 46:1121–3.

Lomen-Hoerth, C., Anderson, T., & Miller, B. (2002). The overlap of amyotrophic lateral sclerosis and frontotemporal dementia. *Neurology*, *59*(7), 1077–1079. https://doi.org/10.1097/WCO.0b013e3283168d1d

Ludolph, A., Drory, V., Hardiman, O., Nakano, I., Ravits, J., Robberecht, W., & Shefner, J. (2015). A revision of the El Escorial criteria - 2015. *Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration*, *16*(5–6), 291–292. https://doi.org/10.3109/21678421.2015.1049183

Lunetta, C., Lizio, A., Sansone, V. A., Cellotto, N. M., Maestri, E., Bettinelli, M., … Corbo, M. (2016). Strictly monitored exercise programs reduce motor deterioration in ALS: preliminary results of a randomized controlled trial. *Journal of Neurology*, *263*(1), 52–60. https://doi.org/10.1007/s00415-015-7924-z

MacIntosh, B. R., Gardiner, P. F., & McComas, A. J. (2006). *Skeletal muscle: form and function.* (Second). Champaign, IL: Human Kinetics.

Martin Ginis, K. A., Latimer, A. E., Arbour-Nicitopoulos, K. P., Buchholz, A. C., Bray, S. R., Craven, B. C., … Wolfe, D. L. (2010). Leisure Time Physical Activity in a Population-Based Sample of People With Spinal Cord Injury Part I: Demographic and Injury-Related Correlates. *Archives of Physical Medicine and Rehabilitation*, *91*(5), 722–728. https://doi.org/10.1016/j.apmr.2009.12.027

Mendell, L. M. (2005). The size principle: a rule describing the recruitment of motoneurons. *J Neurophysiol*, *93*(6), 3024–3026. https://doi.org/10.1152/classicessays.00025.2005

Moholdt, T. T., Amundsen, B. H., Rustad, L. A., Wahba, A., L??v??, K. T., Gullikstad, L. R., … Sl??rdahl, S. A. (2009). Aerobic interval training versus continuous moderate exercise after coronary artery bypass surgery: A randomized study of cardiovascular effects and quality of life. *American Heart Journal*, *158*(6), 1031–1037. https://doi.org/10.1016/j.ahj.2009.10.003

Motl, R. W., McAuley, E., & Snook, E. M. (2007). Physical Activity and Multiple Sclerosis. *Family & Community Health*, *30*(2), 144–150. https://doi.org/10.1097/01.FCH.0000264411.20766.0c

Neeper, S. ., Gomez-Pinilla, F., Choi, J., & Cotman, C. (1995). Exercise and brain neurotrophins. *Nature*, 551–557. https://doi.org/10.1111/j.1365-2990.2010.01093.x

Phillips, M., Flemming, N., & Tsintzas, K. (2009). An exploratory study of physical activity and perceived barriers to exercise in ambulant people with neuromuscular disease compared with unaffected controls. *Clinical Rehabilitation*, *23*(8), 746–755. https://doi.org/10.1177/0269215509334838

Rasmussen, P., Brassard, P., Adser, H., Pedersen, M. V., Leick, L., Hart, E., … Pilegaard, H. (2009). Evidence for a release of brain-derived neurotrophic factor from the brain during exercise. *Experimental Physiology*, *94*(10), 1062–1069. https://doi.org/10.1113/expphysiol.2009.048512

Rejeski, W. J. (1981). The Perception of Exertion: A Social Psychophysiological Integration. *Journal of Sport Psychology*, *4*, 305–320.

Rolenz, E., & Reneker, J. C. (2014). Validity of the 8-Foot Up and Go, Timed Up and Go, and Activities-Specific Balance Confidence scale in older adults with and without cognitive impairment, *53*(4), 2014.

Sharma, K. R., Kent-Braun, J. a, Majumdar, S., Huang, Y., Mynhier, M., Weiner, M. W., & Miller, R. G. (1995). Physiology of fatigue in amyotrophic lateral sclerosis. *Neurology*, *45*(4), 733–740. https://doi.org/10.1212/WNL.45.4.733

Trost, S. G., Owen, N., Bauman, A. E., Sallis, J. F., & Brown, W. (2002). Correlates of adults' participation in physical activity: review and update. *Medicine & Science in Sports & Exercise*, *34*(12), 1996–2001. https://doi.org/10.1249/01.MSS.0000038974.76900.92

Warburton, D. E. R., McKenzie, D. C., Haykowsky, M. J., Taylor, A., Shoemaker, P., Ignaszewski, A. P., & Chan, S. Y. (2005). Effectiveness of high-intensity interval training for the rehabilitation of patients with coronary artery disease. *The American Journal of Cardiology*, *95*(9), 1080–1084. https://doi.org/10.1016/j.amjcard.2004.12.063

Wisloff, U., Stoylen, A., Loennechen, J. P., Bruvold, M., Rognmo, O., Haram, P. M., … Skjaerpe, T. (2007). Superior cardiovascular effect of aerobic interval training versus moderate continuous training in heart failure patients: A randomized study. *Circulation*, *115*(24), 3086–3094. https://doi.org/10.1161/CIRCULATIONAHA.106.675041

Chapter 4

Revising the Research Question

4.1 Introduction

In response to recruitment difficulties described in Chapter 3, this chapter describes a fundamental reworking of my thesis project. I intend to inform the reader on how my immediate reflections inspired a transition in thinking and called for the adoption of a new epistemology. I will then define the philosophical and methodological underpinnings of my new approach to demonstrate how an alternative framework offers the opportunity to formulate telling and meaningful questions related to individual experience. Afterward, I will introduce scholarship from medical sociology and health psychology exploring the study of chronic illness, and locate the study of experience living with ALS in relation to this work. Finally, I will briefly summarize the existing qualitative literature surrounding lived experience in ALS and establish the grounds for exploring my revised research question.

4.2 Personal Reflection

Fourteen months into the intervention study described in detail in Chapter 3, one participant had enrolled and I had increasingly few prospective participants. In a period of reflection, I grappled with reasons for why this project was not working. Initially I generated queries about the rapid time-course of progression, low incidence rates, geographic dispersion of patients and incongruous physical symptomology all of which restrict the window of opportunity for an intervention. Though potentially interesting, these queries all fail to account for why the most successful exercise studies conducted over several years and out of large treatment centres also report small sample sizes and relatively high drop-out rates. *More importantly*, these queries completely erase the individual from the discussion and homogenize the ‘truth’ for each person with ALS. By focusing only on the barriers and facilitators to enrolment, I was unwittingly assuming every person to be equally subject to circumstance; subjects of their physical symptoms, progression rate and geographic location. Not only does this approach problematically erase individuality, it grossly overlooks personal agency and how each person actively negotiates their own lived experience.

Formulating questions of others' individual experience called into question my own experience as a researcher and how my thinking processes are influenced by a set of assumptions and beliefs about knowledge production. It became imperative to recognize how this paradigm influences which ideas I attend to, how I formulate questions and the ways in which those questions are 'answered'. It is therefore important to understand how different epistemologies influence the means of approaching different research questions.

4.2 From Physiology to Phenomenology

Epistemology describes different ways of knowing and learning about the world (Guba & Lincoln, 1994). Many epistemologies have evolved over time and can be distinguished by the assumptions and beliefs they maintain in relation to knowledge production. Post-positivism suggests that there is an objective truth to a given question and that this truth can be attained using the scientific method of inquiry (Guba & Lincoln, 1994). As a student enrolled in a Master of Science program co-supervised by an exercise physiologist, clinical neuromuscular physiologist and clinical neurologist, it should be unsurprising that my research beliefs aligned with post-positivism during the initial phase of this project. We sought to measure the effect(s) of exercise on a certain group of people by using an objective and standardized approach.

Qualitative research on the other hand typically rejects the idea that a single truth can be obtained or measured. Within this realm, several epistemologies including interpretivism and critical theory contend, in different ways, that there are multiple subjective truths that must be considered within the social, cultural and historical context that they were created (Guba & Lincoln, 1994). Rather than minimizing individual differences through group means and the pursuit of a single truth, adopting an interpretivist perspective brings the individual to the forefront of the investigation.

Within the interpretivist umbrella, the philosophy of phenomenology further highlights the individual as expert of their own experience (Ritchie, Lewis, & McNaughton Nicholls, 2013). Emerging from the work of German philosopher Edmund Husserl (1859-1938), modern phenomenology takes on a myriad of philosophical and methodological forms (Lopez & Willis, 2004). Very generally, phenomenology seeks to understand commonalities in the lived experience in relation to a phenomenon for a group of individuals using in-depth interviewing (Smith, 1996). After gathering highly detailed accounts of subjective experience, significant common themes are extracted for analysis. Table 4.1 illustrates differences in the underlying assumptions of two prominent forms of phenomenology (Lopez & Willis, 2004).

Table 4.1 Descriptive and Interpretive Phenomenology

	Descriptive (Transcendental)	**Interpretive** (Hermeneutic)
Major Philosophers	Edmund Husserl (1859-1938)	Martin Heidegger (1889-1976)
Central Tenets	An "essence" of experience can be derived from first-person accounts of lived experience in relation to a phenomenon. Emphasis is given to the **content** of subjective accounts of experience, "what people know about their experience"	An approach that seeks to analyse the context, intention and meaning surrounding a representation of shared experience. Emphasis is given to the **context** and how humans experience the phenomenon rather than what they consciously know about their experience
Assumptions	**Essences:** There are features to any lived experience that are common to all persons who have the experience, referred to as universal essences. **Radical autonomy:** humans are free agents who bear responsibility for influencing environment and culture. **Personal knowledge must be bracketed**: The researcher must shed all personal knowledge to make space for understanding the essential lived experiences of those under study. This	**Bodies are inseparable from the world:** Humans cannot abstract themselves from the world in which they live. Heideigger used the term 'lifeworld' to express the notion that individuals' realities are invariably influenced by the world in which they live. **Situated freedom:** humans are embedded in their worlds to such an extent that subjective experiences are inextricably linked with social, cultural and political contexts. Individuals are free to make choices, but their freedom is not absolute it is constrained by the specific conditions of their daily lives.

	can be termed transcendental subjectivity which means that biases and preconceptions are constantly assessed and neutralized so that they do not influence the object of study. **A true essence:** The research arrives at one correct interpretation of experiences and the essences remain true independent of social location, history and context.	**Personal knowledge is both useful and necessary:** It is impossible to rid the mind of the background of understandings that has lead the researcher to consider a topic worth of research in the first place. Frameworks can be used to interpret and analyse participant narratives. **Co-constitutionality:** Meanings that the researcher arrives at are a blend of the meanings articulated by both participant and researchers within the focus of the study. **Multiplicity of meanings:** There is no one true meaning produced by any interpretive study, but reported findings are logical, plausible and reflect the realities of the study participants

Adapted from (Lopez & Willis, 2004)

As Table 4.1 highlights, there are stark differences in the underlying assumptions and consequent practice of descriptive and interpretive phenomenology. Whereas descriptive phenomenology emphasizes the methodological importance of bracketing (acknowledging and suspending your existing beliefs about a phenomenon prior to its examination) (Allen-Collinson, 2009), the interpretive form rejects the possibility of separating oneself from the understanding of another's experience. Instead, interpretive phenomenology encourages reflexivity, a process of attending to personal knowledge and the ways it may contribute to an understanding. Despite how the 'objectivity' of Husserlian phenomenology resonates with my post-positivist roots, Heidegger's situated freedom and co-constitutionality more appropriately acknowledge that the exploration of meaning is a dynamic process worthy of reflexive attention. It is my personal belief that in the re-telling of a story that belongs to another person, it is disingenuous and egotistical to claim that I could convey the true and sole essence of their experience. Therefore, the interpretive form of phenomenology offers a framework that more closely aligns with my beliefs related to ownership and self-presentation which will be useful in examining lived experience.

In practice, a phenomenologist may focus on the way two people speak differently about what is medically categorized as the same illness because of how each individual interprets their health (Smith, 1996). When conducted in a way that emphasizes the structurally influenced, historically specific and socially situated nature of experience, interpretive phenomenology can be a very powerful tool for understanding the individuality of experience for people who relate to a common phenomenon. By highlighting the social-structural constraints acting upon individuals, interactions and relationships the researcher can explore how individuals exercise their own agency within their specific social context to negotiate their personal experience.

4.4 Interactions, self-identity and choice

Scholars of sociology and psychology have long contended that individuals give meaning to their life, actions and decisions by interacting with the environment (Gecas, 1982). The way in which we relate to others, interact with objects and engage with the physical environment influence how we perceive ourselves (Bandura, 1999). Self-identity then presents a conceptual framework used to guide decisions and negotiate choice. For example, I can choose to ascribe meaning to the time I spend reading peer-reviewed papers from an assigned workspace within the School of Kinesiology and Health Studies as interactions that contribute to my identity as a graduate student. Though this part of my identity arises from contextualized interactions, it is not abandoned when I enter a different environment and continues to influence my choices. Take for instance, a social engagement with friends outside of academia where an unfamiliar but controversial topic comes up in conversation. If I am asked to give my opinion I would probably refrain from creating one based only on the accounts of the other attendees and follow up by learning more after the social engagement ended. In this instance, my identity as a graduate student with experience evaluating sources of knowledge, reading,

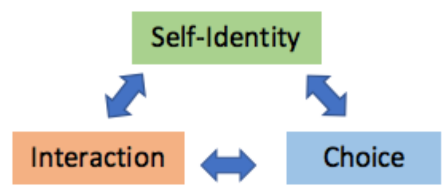

Figure 9. Simplified model of how constructs may influence one another in the negotiation of lived experience

and synthesizing new ideas would influence my apprehension in speaking out about a subject of which I have little knowledge. Though very simplistic, this illustration should emphasize how intimately related our interactions, identity and choices are in the way we experience the world. Importantly, there are complexities to each of these relationships because the choices we make can threaten or reaffirm self-identity which may change how we perceive interactions. The multidirectional nature of these relations is signified by the double-headed arrows shown in figure 9.

4.5 The Study of Chronic Illness

The ideas of interaction, self-identity and choice have long been taken up by scholars of medical sociology and health psychology in the study of chronic illness to understand how people make sense of their selves, interactions and choices in the face of a changing body. In his seminal paper (1982), sociologist Michael Bury conceptualised subjective accounts of living with rheumatoid arthritis as ‘biographical disruption’ whereby chronic illness disrupts personal expectations, plans and the structures of everyday life, requiring “a fundamental rethinking of the person’s biography and self-concept” (1982:169). Along a similar line of thought, Kathy Charmaz (1991) explored ‘loss of self’ through illness and identity questioning. She suggested that the individual’s present identity is compared to that of their past, while simultaneously contemplating identity of the future (Charmaz, 1991). In this way “identity questioning involves wondering if the present identity founded in illness will become permanent and override other sources of identity” (1991:101). As a means of protecting earlier self-definitions, Charmaz suggests that people reconcile themselves to illness by lowering their expectations of self. By recalibrating one’s expectations of what their body is capable of, people can maintain a sense of self and control in their experience.

Similar ideas come up in models of chronic illness within the field of health psychology. For example, the model of adjustment and self-regulation, illustrated in detail by Sharpe and Curran (2006) in a review of chronic illness in health psychology, suggests that an individual appraises the situational meaning of a change from within their existing self-identity and responds by acting in ways that minimize the disruption of the change on their self-concept. Thus, the importance of perceived change, self-identity and choice are emphasized in both medical sociology and health psychology literature.

4.6 ALS: Chronic and Terminal

While medical sociology and health psychology both offer interesting frameworks for understanding how people experiencing chronic illness appraise change, reconcile self-identity and negotiate choice, ALS may not fit seamlessly within these frameworks. As a rapidly progressive and incurable disease, ALS is not only chronic but also terminal, which generates other complexities unaccounted for by most experiences included in chronic illness studies. Testing this applicability, Locock and colleagues recently examined the relevance of Bury's 'biographical disruption' in motor neuron disease (MND; an umbrella term for several neuromuscular disease including ALS) and found that rather than seeing illness onset as an unwelcome disruption to their lives, the construct was more aptly described as 'biographic abruption', the sense that the diagnosis is a 'death sentence' (Locock, Ziebland, & Dumelow, 2009). Although they also found some participants sought to make sense of and find new meaning in their remaining life, a process termed 'biographical repair' (Locock et al., 2009). In both cases, we see that rather than responding to an undesirable disruption and adapting over time to return to a state of normalcy, people experiencing MND recognize that they are not likely to establish a new 'normal'. The differences in reaction between abruption and repair may then be guided by the individual's perceived locus of control. In a narrative study with people living with MND, King and colleagues (2009) found that individuals who perceive that they maintain control over the disease tend to adjust more effectively to illness-related bodily changes while those who feel that the disease is in control adapt less effectively (King et al., 2009). The authors used a grounded theory approach to generate a model of 'ongoing change and adaptation' which emphasizes the cyclic nature of frequent and ongoing reappraisal and adaption as people with MND/ALS experience frequent disease-related bodily changes. The model is included at the end of this chapter as figure 10 and outlines a cyclic process of perception, reaction, appraisal, adaptation and adjustment to a change.

Other qualitative research relating to the construct of choice for people living with MND focuses on decisions surrounding palliative care (Hughes et al., 2005), the use of feeding tubes (Vesey, Leslie, & Exley, 2008) and assistive ventilation (Lemoignan & Ells, 2010; Sundling, Ekman, Weinberg, & Klefbeck, 2017). Table 4.2 summarizes additional relevant studies relating to the experience of diagnosis, QoL appraisal and engagement in daily of activities for people living with MND, for a comprehensive review please refer to Sakellariou, Boniface, and Brown 2013.

Table 4.2 Summary of select studies investigating the experience of ALS

Study	**Aim**	**Design**	**Participants**	**Findings**
Foley, Mahony, and Hardiman 2007	To identify the meaning of QoL in five individuals with ALS	In-depth interviews with five individuals guided by a phenomenological design	5 people living with MND in Ireland	QoL is individual, multi-dimensional and defined by cognitive and behavioural strategies used to cope with ALS. Themes: importance of faith, search for control, importance of dignity, desire to maintain identity, importance of family, sense of loss, importance of altruism and support, fighting ALS and appreciation of life.
Brown and Addington-Hall 2008	To explore patients' experiences and how they talk about living and coping with MND	Longitudinal narrative case studies	13 people living with MND in the UK	Four types of narratives emerged: sustaining (living life as well as possible through keeping active and engaged), enduring (feeling disempowered, unable to fight against death), preserving (focusing on survival) and fracturing (recognizing loss and fearing what is to come).
King, Duke, and O'Connor 2009	To develop of a model explicating the dimensions of change and adaptation of living with MND	Grounded theory based on symbolic interactionism	25 people living with MND in Australia	Participants used a cyclic, decision-making pattern about 'ongoing change and adaptation' as they lived with the disease. Life decisions were negotiated by participants to maintain a sense of self and well-being in the face of change
Pavey, Allen-Collinson, and Pavey 2013	To explore the lived experience and life-worlds of	In-depth interviews guided by a sociological-	42 people living with MND in Australia	Themes: the diagnostic quest, living with uncertainty, hearing bad news, communication difficulties; and a reified body of medical interest

	MND sufferers surrounding the diagnostic journey	phenomenologic al design		
Brott, Hocking, and Paddy 2007	To elucidate the experience of engaging in day-to-day activities from the experience of people who live with MND	In-depth interviews guided by a phenomenologic al design	7 people living with MND in New Zealand	Participants experienced MND in terms of changes in participation in daily life. As the condition progressed, changes in their levels of engagement in activities resulted to the loss of valued social roles
Locock, Ziebland, and Dumelow 2009	To explore how people construct their accounts of living with MND and what they say about their life	Narrative Interviews	35 people living with MND in the UK	People experience MND in different ways; as a death sentence (biographical abruption), as a major disruption to their life (disruption); or as a challenge that they try to make sense of (repair)

Adapted from (Sakellariou et al., 2013)

4.7 Conclusion

To the best of my knowledge, no studies have sought to examine how people living with ALS negotiate decisions related to physical activity and exercise engagement. To make sense of our own failed intervention study, I intend to use an interpretive phenomenological approach to explore subjective accounts of experience related to purposeful movement prior to and following onset of symptoms related to ALS.

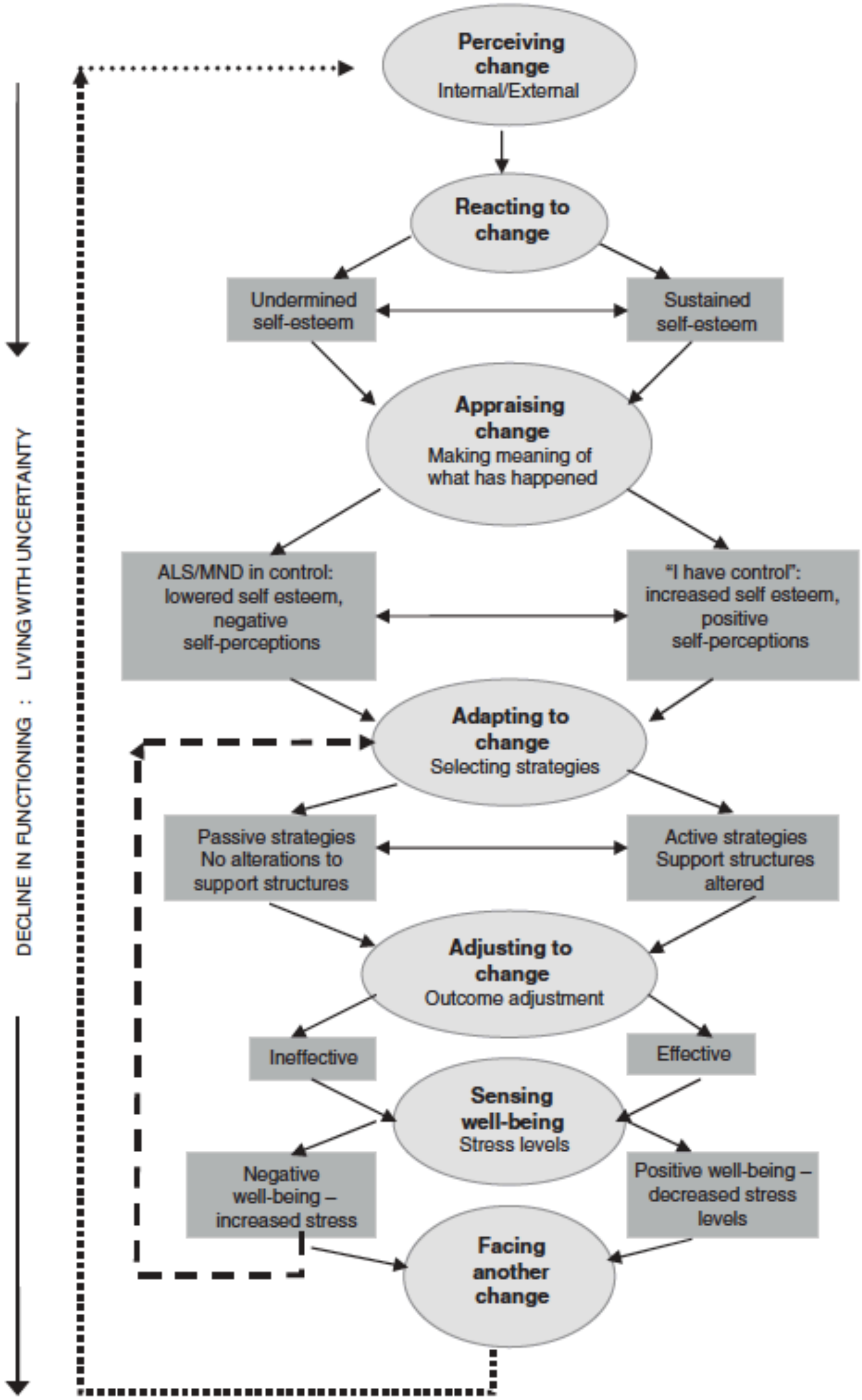

Figure 10. Model of 'ongoing change and adaptation' developed by King et al (2009).

4.8 References

Allen-Collinson, J. (2009). Sporting embodiment: sports studies and the (continuing) promise of phenomenology. *Qualitative Research in Sport and Exercise*, *1*(3), 279–296. https://doi.org/10.1080/19398440903192340

Bandura, A. (1999). Social Cognitive Theory of Personality. *Handbook of Personality: Theory and Research*, 154–196. https://doi.org/10.1016/0749-5978(91)90022-L

Brott, T., Hocking, C., & Paddy, A. (2007). Occupational Disruption : Living with Motor Neurone Disease. *British Journal of Occupational Therapy*, *70*(January), 24–31.

Brown, J., & Addington-Hall, J. (2008). How people with motor neurone disease talk about living with their illness: A narrative study. *Journal of Advanced Nursing*, *62*(2), 200–208. https://doi.org/10.1111/j.1365-2648.2007.04588.x

Bury, M. (1982). Chronic illness as biographical disruption. *Sociology of Health & Illness*, *4*(2), 167–182. https://doi.org/10.1111/1467-9566.ep11339939

Charmaz, K. (1991). *Good Days, Bad Days: the self in chronic illness and time*. New Brunswick, New Jersey: Rutgers University Press.

Foley, G., Mahony, P. O., & Hardiman, O. (2007). Perceptions of quality of life in people with ALS : Effects of coping and health care, (December 2006), 164–169. https://doi.org/10.1080/17482960601164532

Gecas, V. (1982). The self-concept. *Annual Reviews of Sociology*, *8*, 1–33.

Guba, E., & Lincoln, Y. (1994). Competing paradigms in qualitative research. In *Handbook of qualitative research* (pp. 163–194).

Hughes, R. A., Sinha, A., Higginson, I., Down, K., & Leigh, N. P. (2005). Living with motor neurone disease: lives , experiences of services and suggestions for change. *Health and Social Care in the Community*, *13*(1), 64–74.

King, S. J., Duke, M. M., & O'Connor, B. A. (2009). Living with amyotrophic lateral sclerosis/motor neurone disease (ALS/MND): Decision-making about "ongoing change and adaptation." *Journal of Clinical Nursing*, *18*(5), 745–754. https://doi.org/10.1111/j.1365-2702.2008.02671.x

Lemoignan, J., & Ells, C. (2010). Amyotrophic lateral sclerosis and assisted ventilation : How patients decide. *Palliative and Supportive Care*, (8), 207–213. https://doi.org/10.1017/S1478951510000027

Locock, L., Ziebland, S., & Dumelow, C. (2009). Biographical disruption, abruption and repair in the context of motor neurone disease. *Sociology of Health and Illness*, *31*(7), 1043–1058. https://doi.org/10.1111/j.1467-9566.2009.01176.x

Lopez, K. A., & Willis, D. G. (2004). Descriptive Versus Interpretive Phenomenology: Their Contributions to Nursing Knowledge. *Qualitative Health Research*, *14*(5), 726–735. https://doi.org/10.1177/1049732304263638

Pavey, A., Allen-Collinson, J., & Pavey, T. (2013). The lived experience of diagnosis delivery in motor neurone disease: a sociological-phenomenological study. *Sociological Research Online*, *18*(2).

Ritchie, J., Lewis, J., & McNaughton Nicholls, C. O. R. (2013). *Qualitative research practice: A guide for social science students and researchers*. Sage.

Sakellariou, D., Boniface, G., & Brown, P. (2013). Experiences of living with motor neurone disease: a review of qualitative research. *Disability and Rehabilitation*, *35*(21), 1765–1773. https://doi.org/10.3109/09638288.2012.753118

Smith, J. A. (1996). Beyond the divide between cognition and discourse: Using interpretative phenomenological analysis in health psychology. *Psychology & Health*, *11*(2), 261–271. https://doi.org/10.1080/08870449608400256

Sundling, I., Ekman, S., Weinberg, J., & Klefbeck, B. (2017). Advances in Physiotherapy Patients ' with ALS and caregivers ' experiences of non-invasive home ventilation, *8196*(July). https://doi.org/10.1080/14038190701803351

Vesey, S., Leslie, Æ. P., & Exley, Æ. C. (2008). A Pilot Study Exploring the Factors that Influence the Decision to have PEG Feeding in Patients with Progressive Conditions, 310–316. https://doi.org/10.1007/s00455-008-9149-0

Chapter 5

Living and Exercising with ALS: Exploring a Progress Paradox

5.1 Introduction

Exercise is modestly beneficial for maintaining physical function and conditioning for people living with ALS; however, very few controlled intervention trials have been conducted and most feature small sample sizes (Dal Bello-haas, Florence, & Krivickas, 2013). Combined with the author's personal experience of recruiting only one participant to an exercise trial over an 18-month period despite access to ALS patients and persistent efforts, it appears that there are challenges to recruitment for exercise trials in this population. To more thoroughly understand possible barriers to study enrollment, it is useful to listen to first-hand accounts of people living with ALS.

A small number of phenomenological studies have explored the illness experience of motor neuron disease and ALS, although most maintain a medical focus exploring patient-centered experiences of palliative care (Hughes et al., 2005; Lemoignan & Ells, 2010; Sundling et al., 2017; Vesey, Leslie, & Exley, 2008). Several reports have explored accounts of everyday experience like engaging in occupational activities and how individuals give meaning to quality of life (Brott, Hocking, & Paddy, 2007; Foley, Mahony, & Hardiman, 2007) and have observed common themes surrounding the sense of loss, search for control and desire to maintain social roles in the face of a changing body (Brott et al., 2007; Foley et al., 2007). However, no studies have examined how people with ALS negotiate ideas and decisions related to exercise or, more generally, physical activity.

It is speculated that the everyday experience of living with a progressive and terminal neuromuscular disease has significant implications for how someone thinks about and engages with exercise. The purpose of the present study is therefore to explore everyday experiences of individuals with ALS to better understand how their lived experience impacts the ways they engage in physical activity and exercise. Developing an understanding of how people with ALS experience this phenomenon will present possible explanations for the limited recruitment of past intervention trials and reveal important considerations for the design of future studies and interventions utilizing exercise as a therapeutic treatment.

5.2 Methods

5.2.1 Research Design and Methodology

To better understand the experience of living with ALS, and the ways it impacts engagement with physical activity, it was essential to listen to personal accounts of those who have experienced this phenomenon. The study was guided by interpretive phenomenology which is concerned with understanding the world as people experience it rather than how they make sense of individual experiences (Brott, Hocking, and Paddy 2007). To gather meaningful data, semi-structured interview questions asked participants to describe their lived experiences and share personal stories.

5.2.2 Ethical Considerations

Two major ethical considerations influenced how the study was conducted; the first recognized the sensitivity of disclosure. Speaking about the experience of living with a chronic and terminal illness would likely involve talking about topics that are considered sensitive and private. At the beginning of the interview, the voluntary nature of participation was emphasized to each participant and the option to decline any question or withdraw at any time was understood. On just one occasion, when a participant appeared silently apprehensive and emotional in response to a question, the interviewer responded by gently reminding the participant of the option to decline and they chose to forego the question. After the participant was given a moment to collect their thoughts, they agreed to continue with a new question.

The second ethical consideration was participants' privacy. Participants were assured that their personal information would be kept confidential and their identity anonymized as thoroughly as possible. Given the relatively small group of people living with ALS in this geographic area, participants understood that absolute anonymity could not be guaranteed however considerable efforts were made to protect their identities as best as possible. Participants were each given a pseudonym and other identifiers like locations, names of people discussed, and certain relationships were altered.

5.2.3 Recruitment

A convenience sample of six participants diagnosed with probable or definite ALS were recruited from a local rehabilitation hospital and one additional participant was recruited through word of mouth. Inclusion criteria included: conversational English language skills, although verbal communication was not necessary. Those with dysarthric symptoms that significantly impaired the ability to speak were invited to write or type answers, or designate a speaker. One prospective participant declined participation due to the additional efforts required to write or type, and another elected their spouse to speak on their behalf as they nodded or shook their head to corroborate responses shared on their behalf.

5.2.4 Data Gathering and Analysis

Data gathering occurred via semi-structured, in-depth interviews conducted at a time and place that was convenient for each participant. A semi-structured approach afforded the interviewer the flexibility to follow-up novel ideas and topics shared by participants that were not included in the original interview guide (see appendix F), and most interviews strayed from the structure of the included topic guide. Since most participants travelled a considerable distance from their place of residence to attend the clinic in Kingston, it was convenient for nearly all participants to coordinate interviews with pre-existing appointments. Thus, five of the seven interviews occurred following an appointment with their neurologist, in the presence of one or two caregivers. The two other participants were interviewed individually at a time and place of their choice, one chose to use video-teleconferencing (i.e. Skype) while the other travelled to Queen's campus. Interviews ranged in duration from 20 to 60 minutes and each audio recording was transcribed verbatim within 48 hours of the meeting. Analysis commenced immediately following the first interview with reflection on the topics addressed in preparation for following interviews. Although member checks were offered to all interviewees, only one participant expressed interest in reviewing their transcript, all others declined. The reviewed transcript was returned with small grammatical changes and removal of sections of some stories. Inductive thematic analysis was then carried out (Braun & Clarke, 2006; Braun, Clarke & Weate 2017), which involved reading and in-depth re-reading of transcripts followed by extraction of significant statements and salient themes through a process of 'horizontalization' where themes are extracted and assigned the same level of importance before being organized into hierarchical themes and sub-themes (Yuksel & Yildirim, 2015). Significant statements were individually printed and physically sorted into groups of 'shared meaning'. These groups of meaning and individual significant statements were then discussed with two colleagues capable of critiquing the author's ideas and offering alternative viewpoints. Following several iterations of physical sorting, memo-writing and written analysis, the author identified three major themes which are presented in the analysis below.

5.3 Findings

The seven participants were four men and three women aged between 50 and 75 years old, and mean time since diagnosis was 20 months excluding one participant who was diagnosed more than twenty years earlier and is clinically recognized as an exceptional case. Participants resided between 10km and 125km from the neuromuscular clinic and most lived with a spouse with one living with their son. Two participants were independently mobile and required little assistance, three used mobility aids (i.e. four wheeled walkers) and required some assistance, and two used wheelchairs for mobility and required assistance with most daily tasks.

During analysis, three major themes were identified as being common to the experience of living with ALS and were represented to varying degrees in the accounts given by each participant. The first, 'Living in a changing body' refers to the ways in which a body subject to ongoing and uncontrollable change impacts the participant's everyday life which came together through the subthemes *bodily uncertainty, protecting the self,* and *self as expert*. The second theme 'Environmental access' captures how the interactions between the participant and their environment transform over time and are mediated by physical access, financial access and caregiver support. The third theme '(f)utility of exercise' relates to how individuals negotiate the value of exercise for a body affected by ALS. Importantly, the themes and subthemes explored below describe experiences that do not personally belong to the author, with the intention of having participants tell their own stories direct quotations are used as often as possible. Each quote has been assigned an identifying number according to the order in which they appear e.g. Q1, Q2 etc. for ease of reference throughout the discussion in section 5.5.

5.3.1 Living in a changing body

5.3.1.1 Bodily Uncertainty

Living with ALS means living in an unpredictable, changing body. The illness experience marks a transition from bodily 'dis-appearance', a body mostly unnoticed by the conscious mind to bodily 'dys-appearance', a dysfunctional body subject to acute attention (Williams, 2000). As Brian explained;

> "There are things like, something, I don't know maybe a tickle in your tongue and right away you notice it. Or- I don't have much in the way of fasciculations now but once in a while I'll think my cell phone's going off in my pocket and I reach in and there's no cell phone" (Q1)

The unsolicited appearance of bodily changes can bring the erratic body to the forefront of the mind. Other times, heightened awareness comes from uncertainty about whether the body will respond to a command, "…every morning I'd get up and I'd put both feet on the floor and think 'wonder if they're gonna work today' you know?" (Brian, Q2). Most prominently, attention to bodily control arose from accounts of the physical function required for activities that bring meaning to someone's life. According to Walter, "My garden is the best hobby I have and still do" (Q3). Dorothy related her disease to the ability to keep up with her typical activities, she explained that, "I go to church three times a week. Twice on Sunday, and Wednesday night. It [ALS] hasn't slowed me down yet." (Q4). Stories relating to function were often accompanied by the words "still" and "yet" which suggest that people recognize the body's inability to perform activities it once did, while anticipating loss of function in the future. In this way, people appear to be expecting further dysfunction and increased unreliability, though much less certain as to *when* these changes will occur. Remarks about the body as unusual and feeling uncertain of its capabilities in the future are captured by the notion of *bodily uncertainty.*

5.3.1.2 Protecting Self

In a progressively uncertain body, individuals develop a heightened responsibility to protect the self from harm. In a physical sense, this involves recognizing the potential for the physical body to threaten its own safety and wellbeing. Norman explained how his respiratory weakness can threaten his safety when driving independently,

> "I still have a driver's license, I have no prohibition on driving but at times I've not been comfortable with driving because I now sleep with a BiPAP machine. Sometimes I would get midday and feel this desire for what I refer to as 'mask time', because I would start to feel groggy. So the point I was making there, at times I don't feel comfortable driving from a safety perspective" (Q5)

Similarly for Brian, controlling and coordinating his feet lead to concerns about the risk of falling, "I'm still really heavy on my feet, I do worry a bit about tripping although I don't go very fast" (Q6). In efforts to protect the self from physical harm, people withdraw from or modify activities. Sometimes this involves employing adaptive equipment or personal support from a trusted companion. Alice, who experiences weakness in one arm was considering trying an AquaFit class, but she was uncertain about controlling her body in the water:

> "I think balance would be one thing, unless you had a noodle or some type of floating device that would help me out. I mean, we did go to our pool in our complex and I just kind of floated around on the noodle, but there was always someone close in hand" (Q7)

Here, the possibility of feeling unstable in the water threatens Alice's safety and would need to be addressed before she would feel comfortable engaging in the activity.

Not only do limitations of the body threaten the physical self, feeling powerless over an erratic body can lead to feelings of inadequacy and a devalued sense of self (Charmaz, 1991). For instance, Brian played on a varsity sports-team and continued playing competitive team sports well into his middle-aged life, "I will admit, I'm still self-conscious. I used to be a pretty good athlete you know, to be the slowest, the worst, it's a little tough." (Q8). Brian's sense of self as a competent athlete is threatened by a body no longer capable of performing the activities associated with that part of his identity. He described this by saying, "I'm a little dismayed at what I can lift now." (Q9). For others, the erratic body stripped away career-related identities. Dorothy experienced significant weakness of the muscles responsible for speech, "The worst thing about this is I had to quit work early, earlier than I wanted to. I worked in an office…I would have to make technical phone calls and people couldn't understand me" (Q10). Unable to conduct necessary tasks at work, Dorothy was required to renounce her identity as a working person before she was emotionally prepared to, and instead take on a new identity demarcated by disability. Among the cultural discourse of disability are judgments about competence, capability and independence which were particularly degrading to Dorothy's self-worth. Furthermore, losing a career-related identity can be exceedingly harmful to the emotional self because it requires public disclosure of personal losses. Breaching the boundaries between public and private introduces a new level of vulnerability for the emotional self (Charmaz, 1991). For one participant who requires assistance transferring in and out of his wheelchair, his personal matters can become very public unless properly supported by another person. Harvey explained, "I can't go [to the appointment by] myself cause if I've got to go to the washroom when I'm there or on the way there…I've got to do it in my pants. You see what I mean?" (Q11). Harvey's body unintentionally puts him at risk of embarrassment and feelings of ineptitude when these cultural boundaries are crossed. Therefore, to protect himself from the possibility of personal discomfort and public embarrassment, Harvey accepts the role of care recipient, planning outings around caregiver availability. As Charmaz (1991) eloquently summarizes "the problems with which ill people struggle are existential; their solutions are often organizational" (1991: 138).

5.3.1.3 Self as Expert

Despite sharing the same diagnosis, the physical experience of ALS is unique for each person. Within the sample of seven participants there were numerous visible differences in clinical presentation. Two participants experienced substantial dysarthria and feeding difficulties but little to no functional weakness in the upper and lower limbs. Another three participants featured mild dysarthria, some upper and/or lower limb weakness, and two of them noted respiratory limitations. The remaining two individuals had no use of their lower limbs, substantial neck weakness and some upper limb difficulties. Within a relatively small sample of individuals, there was considerable variability in the physical manifestation of disease. Emphasizing individuality further, several participants reported living with other medical conditions in addition to ALS. Harvey explained, “I also have severe rheumatoid arthritis. I’ve had that for about ten years. I thought it was the arthritis but it was ALS creeping up on me.” (Q12). The physical experience of ALS is then further specialized by bodily changes related to other causes. Thus, on a physical level the bodily changes experienced by each person are different and more importantly, *how* each person gives meaning to their physical experience is different. Walter explained, “I’m the one to say when I can, when I can’t, and it’s going slowly, slowly, slowly, slowly. I try to push it as much as I can but when it gets there…”(Q13) and Alice shared, “I asked [my neurologist] was there anything specific that I should or shouldn’t do and he said ‘No, not really. Your body will tell you when it’s tired and listen to it’” (Q14). Only the person living in the changing body can truly understand their experience and therefore have expert knowledge about their body.

In relation to fatigue specifically, each person responds to physical demands in different ways. Regarding his upright position while attending the neuromuscular clinic, Harvey explained his anticipated fatigue:

> “When I go home tonight, I’m gonna be whipped…I require a neck rest for my head. I can barely hold it up for ten minutes at home. I’ve been holding it up since 1 o’clock” (indicating a duration of more than one hour) (Q15)

Harvey perceived his fatigue to stem largely from neck weakness, while Alice reported fatigue in relation to respiratory weakness:

> Alice- "We have the dog, she always has a walk in the morning...depending on the weather if I'm able to go out with them. I do try. They go ahead of me and that's all right"
> Spouse- "When we come back Alice lies down, because her breathing is somewhat affected"
> Alice- "I push the walker so I think that tends to wear you out a bit more too" (Q16)

In different ways, fatigue emerged as a common thread throughout all participant accounts; feeling chronically fatigued from the weakening body, acutely tired following an activity or emotionally exhausted from mental processing. Each form of fatigue and the ways that they interact are considered when the expert self decides which physical efforts are worth the ensuing fatigue. As Dorothy explained, "Mondays I'm usually tired from being out twice on Sunday, but that's a small price to pay (smiles)." (Q17). When the physical efforts are related to something meaningful for that person, fatigue is perceived to be well worth it. However, when the activity has no personal significance the 'return' is likely not worth the participatory effort and resulting fatigue. When asked to think about the possibility of riding a stationary bicycle in a spin class, Alice responded, "I think probably not, I don't think I have the wind for it…I could do a few pedals but then I would be wiped, and I would be wiped for a couple days possibly" (Q18). Based on an intimate understanding of her physical body and respiratory capacity, Alice was quite certain about how her body would tolerate and respond to the physical demands of cycling.

Using personal and bodily expertise, individuals negotiate decisions and authorize engagement with certain physical activities. An additional intricacy emerges here since exercising this authoritative voice can be more difficult for some than others. Those who experience severe dysarthria have difficulty communicating their bodily sensations with others and unless appropriately supported there is the risk of feeling entirely powerless and disembodied. Sheila's spouse recounted the early days of physiotherapy for his wife whose speech is now unintelligible.

> "When we first started going there, the physiotherapist was still trying to get a grip on how much Sheila could do and how much she couldn't…she can draw the answer out of Sheila by talking to her and Sheila will nod yes or no." (Roger, Q19)

When asked if she enjoyed going to the physiotherapist, Sheila nodded yes. Despite being limited in her communication, Sheila's physiotherapist treated her as the expert of her own body which appears to be very important in supporting the person's feelings of self-worth and personal control. This illustration was included to demonstrate further how changes in the physical body create very different experiences for each person in their life with ALS. Whether physically, emotionally or existentially, no two bodies experience ALS in the same way.

5.3.2 Environmental Access

Whether an individual can engage in the activities they feel are personally appropriate and worthwhile is mediated by how the body interacts with the environment. For some, physical access directly limits engagement with desired activities. Dorothy enjoyed taking part in twice weekly exercise classes at her apartment building; however, she will soon move in with her son, Jason, for additional support, "Jason lives in the country so it's going to put a limit on the exercise I can do." (Q20). For Walter, his limited mobility impacts the types of exercise machines he can access:

> "I wish to have more but it's impossible because they have nice machines but I cannot be transferred from one to another because there's no lift and I cannot do it- it's very dangerous to transfer." (Q21)

While Harvey's mobility limitations and lack of adaptive equipment prevent him from easily leaving his home, "The access bus won't help you up and down stairs. I can't get a lift for my wheelchair yet, this is all in the works but I've been waiting since Christmas and I've deteriorated" (Q22). Evidently the relationship between the body and physical environment impacts how readily someone can engage in the activities of their choice and this relationship can be mediated by financial resources. In some cases, finances facilitate engagement in physical activity like when personal capital allows someone to purchase home exercise equipment, as noted by three participants. With regular physical access to appropriate equipment, activity engagement is influenced by motivation, as the spouse of a participant described:

> "We go downstairs in the evenings to watch TV, the bike sits in the rec room. There's no reason why I or Sheila couldn't get on the bike and watch TV from the bike for 15 minutes or 10 minutes or 5 minutes. It's a case of doing it." (Roger, Q23)

For others, finances directly limit physical access, "I can't afford to be buying equipment and all this care, I haven't worked in years and [my wife] is the only one working and she's been off for a year and a half." (Harvey, Q24). Harvey has been waiting for several months to receive a motorized wheelchair and lift, and while he waits, the expenses continue to accumulate,

> "When I go to the doctor it costs. For a trip down to [the neurologist's] office and return it's 90 bucks" which pays for "a taxi cab and he will help me in and out of the house. Nobody else will take the responsibility going down the stairs" (Q25)

Despite experiencing comparable mobility limitations and residential location to another participant, Harvey's access is substantially reduced because of financial barriers. It is therefore important to attend to how specific factors impact each person and their ability to engage in desired activities differently.

In addition to finances, caregiver support emerged as an important element of environmental access. Many participants described feeling supported by friends and family living close by who facilitate access to their activities of interest, "I can get there any day because if Jason has to work, my sister will pick me up and take me" (Dorothy, Q26). However, while friends and family may be highly supportive and willing, other responsibilities and commitments can limit how well their intended support translates to active facilitation. Norman spoke about his experience, saying "It means coordinating with my wife to make sure I get to these things which is not always easy. She's been very supportive but it's not always easy" (Q27). For Harvey, his wife's availability is extremely limited "She's gone from 8 in the morning till 6 at night" (Q28). It is also important to consider how finances and caregiver support intersect for some individuals. One participant recently received Direct Funding, a government assistance program for adults with physical disabilities to employ personal care attendants. Fortunately, this funding allows for regular and reliable caregiver support, "she works five and a half hours a day, 7 days a week" (Q29). However, the application and approval process for this program can be long, arduous and ultimately unsuccessful for others. Without the financial means to employ personal support workers (PSWs) out-of-pocket, people who require assistance for most daily activities are further limited by caregiver availability. Harvey explained how finances, equipment dependency and personal support requirements collectively restrict his ability to access a local appointment,

> “I have to see my other doctor in July, if I don’t get this resolved I can’t go. I’m not throwing out a hundred bucks to go down there, no way. And then if it’s not on a Tuesday when I’m paying for the PSW, I’m gonna have nobody, or my wife is gonna have to take a day off work which they’re getting tired of” (Q30)

Though this excerpt highlights the ongoing frustrations Harvey experiences in relation to his physical, financial and support related access, it is important to share that he is incredibly well-humoured and actively seeks out solutions to problems as he understands them.

In summary, each of the seven participants experienced physical, financial and support related access in their own way. The act of negotiating the impact of these factors on the individual’s ability to engage in desired activities also occurred on an individual basis. Even though some barriers appear to be common to the experience of living in a body with ALS, it should be emphasized that the same barrier can take on very different meanings for people equipped with different resources.

5.3.3 (F)utility of Exercise

The final salient theme revolved around attitudes towards exercise and its usefulness for someone whose motor neurons are progressively dying. Some participants spoke of how they are in some way defined by their engagement with physical activity. As Roger explained, “Sheila has always been an active person” (Q31) and continued engaging in modified physical activities despite the bodily changes. In relation to exercise Roger reported feeling,

> Roger- Positive. We’re still positive, we’re just…
> Danielle (daughter)- Limited.
> Roger- Little bit limited, that’s all.
> Sheila- *teared up (Q32)

Others spoke of how they came to understand the value of keeping physically fit, as Norman described,

> I've always thought of exercise as being related to bodily health I mean and that even in the military is made clear to you and requiring you to annually pass not only a physical fitness test but also taking an annual medical and they were associated. So, I guess after 28 years you start to see the medical benefit factors for exercise and so that certainly did continue in my perspective, as I say, when you go to a health club at six in the morning, I enjoyed it and it just seemed normal, old habits die hard. (Q33)

Participants recounted their lifelong experiences and attitudes towards exercise which became important in contextualizing how they negotiated a common and challenging conundrum; what does exercise mean for a body that is deteriorating? There are strong, competing narratives surrounding physical progress for exercise and ALS. On one hand, cultural discourses tell us to expect the body to become better, faster and stronger with training. On the other hand, the physical loss of motor neurons underlies progressive weakness, functional decline and increasing dependence. Walter explained,

> ALS, my doctor is telling me is very slow progressing, but it's progressing. In 2015 when I was there the first time they put me at level 5 on the [acted out using the lat pulldown machine]. And goes down, down, down, and now I'm on number 3. So, from 5 to number 3 so that tells me that the progress of my disease is progressing, there's not much you can do. I can't force myself to push more than I can because there's problems in my shoulders or my body, so that's, my body as my disability goes, so you gotta change my uh- exercises as well, because I do not have much strength like I used to have. So there's not much you can do about the ALS…(Q34)

Though Walter highlights the futility of exercise in the face of dominant bodily changes from ALS, for him, it does not discount the personal benefits that he finds bring meaning to his life,

> I think that exercise was the best thing of everything, even the professionals say it and even I can feel better about myself. It's hard [motioned to his arms to act out sore muscles] but then it relaxes after I finish and I get tired, little bit tired. So it makes me feel good, the exercise is the best thing I have, and for anybody that has this disease or other disease that you know, you've got to keep moving, there is no other way to do it (Q35)

From Walter's story, it appears that the benefits of exercise extend beyond the physical body and despite measured outcomes decreasing over time, Walter feels that continuing to exercise is worthwhile. Roger echoed this sentiment in saying that "it's good because it makes you do something" (Q36). Though exercise cannot permanently reverse bodily changes resulting from the neuromuscular disease, some people continue to find value and meaning from staying physically active.

In conclusion, for the participants in this study living in a body that is increasingly unreliable impacts everyday life and self-concept. People with ALS have important insights and expertise about their own bodies that should be valued equally to, if not more than, outside expert knowledge. Though there are inherent similarities to living with a chronic and terminal illness, no two bodies experience barriers or facilitators to exercise in the same way. Finally, people independently assign value to the perceived benefits of exercise on their own terms.

5.4 Discussion

The purpose of the present study was to explore everyday experiences of people with ALS, as well as their attitudes, perceptions and perceived barriers and facilitators to engaging in physical activity. This exploration was carried out to better understand how ALS patients' lived experience impacts the ways they engage in physical activity and exercise. The findings of the current study suggest that people with ALS actively and *individually* negotiate what it means to live in a changing body, access activities of interest, and evaluate the usefulness of exercise. Although the results highlight the immense variability and individuality amongst people with ALS and their experiences with physical activity and exercise, common themes are identified that may help clinicians and investigators devise more useful and realistic exercise interventions.

5.4.1 The Erratic Body

One common theme highlighted in the present study was that individuals with ALS experienced frequent bodily reminders of illness (e.g. increasing weakness, muscle fasciculations) which lead to feelings of uncertainty about how and when the body will fail. People with motor neuron disease similarly perceive their bodies to be unreliable (Brott, Hocking, & Paddy 2007) and acutely attend to ongoing and progressive loss of function, strength and ability (Brown & Addington-Hall, 2008). Continuously questioning the body's capabilities deterred participants in the present study from engaging in activities that demand coordination, strength and endurance (ref Q18). For people with ALS, feeling unable to participate in certain physical activities because of disease related limitations can be emotionally taxing.

One source of emotional distress revealed in the present study was the reconciliation of new and former identities (ref Q8). Losing the ability to perform physical tasks that once defined a social or career role was troubling for participants' sense of self (ref Q10). Levins and colleagues (2004) found that individuals with spinal cord injuries (SCI) similarly endured identity questioning following injury because self-identity was strongly connected to the physical activities they were no longer capable of performing (Levins, Redenbach, & Dyck, 2004). For some people with SCI this involved withdrawing from all forms of physical activity for a period of time following rehabilitation (Levins et al., 2004). Encouragingly, in the present study most participants who expressed the importance of a past identity related to physical activity continued to participate in the same or started new physical activities, despite their changing bodies. For people with ALS in general, past physical activity enjoyment might be a source of motivation for continued exercise and an important consideration for the design and implementation of future exercise interventions.

5.4.2 Environmental Considerations

Evident in the accounts described in 5.3.2, considerable efforts are often required to coordinate the time, transportation, energy and personal support to attend physical activity and exercise engagements outside of the home. In a qualitative investigation of exercise for people with multiple sclerosis (MS), participants expressed similar environmental barriers and frustrations (Horton et al., 2015). Though different in pathology and prognosis, people with MS experience similar physical limitations, including weakness and fatigue, as individuals with ALS. People with MS described an 'opportunity cost' for engaging in formal exercise because it draws from their limited energy stores than often need to be conserved (Horton et al., 2015). This notion resonates with subjective accounts described by the subtheme *self as expert* where participants undertook a cost-benefit analysis for activities like going to church and feeling tired the next day (ref Q17) or pedaling on a stationary bicycle only to feel exhausted for days afterward (ref Q18).

In another study looking at leisure time physical activity engagement for individuals with neurological conditions like muscular dystrophy, MS, motor neuron disease and Parkinson's disease, Elsworth and colleagues (2009) reported that cost and limited access to suitable facilities, equipment and transportation were all noted as barriers to participation. Similar factors were pertinent for individuals with SCI, although Kehn and Kroll (2009) emphasized how a single factor rarely facilitates or constrains physical activity, instead a cluster of intertwining factors mediate participation for people with SCI. The present study also observed how the interaction of financial resources and caregiver support can both facilitate (ref Q26, Q29) or hinder (ref Q20, Q26, Q27) participation and that these interactions are experienced differently by each person with ALS. For example, two participants in the present study featured similar physical manifestations of disease and lived a comparable distance to an accessible exercise facility, yet they reported considerably different levels of participation in exercise. One participant described having access to a motorized wheelchair, in-home lift, accessible transportation and external PSW support, all of which facilitated their participation in a twice weekly exercise program at a nearby facility. Another participant was without adequate assistive equipment, accessible transportation or the financial means to pay for PSW support while their primary caregiver was occupied during day-time hours. Without personal support for transfers in and out of the wheelchair, this participant experienced great difficulty leaving their home and was not physically active. Thus, participants with available income (or adequate external financial help) and social support (i.e. able bodied spouse or child;

or external PSW support) were more able to participate in physical activity regardless of how their self-identity or values related to exercise.

5.4.3 Evaluating the Usefulness of Exercise

Interestingly, the present study found that despite observable progressing weakness while exercising regularly, some people with ALS continued to exercise. This is markedly different from physical activity cessation typically observed in people pursuing weight-loss goals with little to no success (Elfhag & Rössner, 2005). It is possible that continuing to exercise despite noticeable weakness allows people with ALS to focus on the positive aspects of their mobility (Elsworth et al. 2009) and gain some of the psychosocial benefits (e.g. improved confidence and felt normality) reported by people with MS following six weeks of resistance exercise training (Dodd et al., 2006). Exercise may also offer the opportunity to feel some degree of control over the unpredictable body, an effect highlighted by King and colleagues (2009) who found that when participants with motor neuron disease found ways to incorporate a disease related change into daily living, they regained a sense of being back in control (King, Duke, & O'Connor, 2009). For individuals with ALS interviewed by Foley and colleagues (2007), the search for control, whether through physical performance or knowledge acquisition, was important for their quality of life. People with ALS in the present study felt that there was value to exercise beyond and despite physical changes; this value is likely derived from improvements for psychosocial well-being.

Described by the subtheme *self as expert*, participants recognized having a unique perspective for evaluating the usefulness of exercise and other therapies recommended by experts in health care (ref Q13, Q14). Equipped with highly specialized knowledge about their body's physical capabilities, co-morbidities, energy levels and experience, participants were uniquely positioned to negotiate decisions related to exercise. How fatigued they feel on that day (ref Q17, Q18), how easy or difficult certain movements feel (ref Q19) and how long it will take to recover from an activity all represent important factors to consider for ALS specific exercise programs. Further, some individuals with ALS in the present study also experienced co-morbid conditions that affect their energy levels, pain tolerance and physical abilities. Because each person with ALS experiences the disease differently and insight to this experience can only be accessed by consulting the individual, it is critical to confer with the unique person in designing an exercise program for their benefit.

In conclusion, individuals with ALS evaluated the usefulness of exercise from a unique and internal perspective. For the physical and psychosocial benefits of exercise to be perceived as worthwhile, the activities must appropriately accommodate the needs understood and expressed by the individual.

5.4.4 Implications for Exercise in ALS

Together, the present findings point to several implications for exercise programs and interventions designed for people with ALS. First, the physical demands of the exercise protocol must accommodate the needs of individual bodies. As simple as this sounds, traditional intervention models rely on the assumption that the bodies under study are relatively homogenous in order to detect differences in measured outcomes (Berg & Latin, 2008). The testing and training protocols are also developed and approved prior to study recruitment and standardized for each participant thus eliminating the ability to tailor the intervention to individual needs of individual participants. In the study described in Chapter 3, the cardiorespiratory fitness test required individuals to breathe through a mouthpiece while using their lower limbs to cycle. Several prospective participants had lost the ability to use their lower limbs and thus could not perform the necessary cycling, and others experienced weakness of the muscles around their mouth and felt apprehensive about wearing the mask because they would need to breathe through their mouth only. Though these physical manifestations are not uncommon (Kiernan et al., 2011) they were not foreseen as substantial barriers at the time that the study was designed. Evidently, the pre-set experimental procedures limited recruitment because those procedures could not appropriately accommodate different manifestations of ALS (e.g. lower limb vs upper limb vs bulbar predominate weakness). Ultimately, the assumptions about the homogeneity of bodies with ALS led to the development of an exercise intervention that was appropriate only for a subset of the population, an oversight common to each ALS exercise trial to date (Dal Bello-Haas et al., 2007; Drory et al., 2001; Lunetta et al., 2016).

Limited in different ways, most people with ALS cannot easily or independently attend appointments outside of the home (Phillips, Flemming, & Tsintzas, 2009). Factors like distance to the facility, access to appropriate transportation, caregiver availability, coordinating appointments and accommodating general fatigue interact differently for each person and collectively influence physical access (Elsworth et al., 2009; Kehn & Kroll, 2009). Barriers to participation may be reduced for some individuals with ALS if the intervention allowed for home-based assessment and training. Studies in adults with Parkinson's Disease (van der Kolk et al., 2017) and obese pregnant women (Ong et al., 2009) suggest that the provision of appropriate exercise equipment and some form of accountability whether in-person or remote, were important for training success. This model could be used for people with ALS where kinesiologists, physiotherapists or researchers conduct home assessments, provide equipment and supervise home-based exercise sessions on a regular basis. It is possible that eliminating logistical coordination, efforts and stress involved in leaving the home might allow some individuals to exercise at their desired frequency. Understandably, this design may not be feasible for small research teams or clinical groups with limited funding and more remote supervision might be more appropriate. In any case, future exercise interventions and programs should more closely attend to the myriad of factors that influence physical access for prospective participants.

Finally, exercise engagement and study participation is more likely to be successful when the perceived benefits of participation are personally valued and are not derived elsewhere (Wigfield & Eccles, 2000). As researchers who perceive our work to be inherently worthwhile and healthcare professionals with a vested interest in physical outcomes, we assume that participants have something to gain by taking part. The author speculates that these benefits can take the form of physical improvements in function or fitness, psychological development by accepting a new challenge or perhaps the altruistic feeling of donating irreplaceable time. Charmaz (1991) found that ill people organize their lives by evaluating what they can do and the importance of doing it, and then make trade-offs to eliminate the unnecessary. This organizational process was evident in the present study as several participants who openly valued the physical and psychosocial benefits of exercise had arranged their lives to satisfy those needs elsewhere, like regularly attending physiotherapy or an existing structured exercise program. Consequently, these people felt they had little additional benefit to gain from taking part in an exercise intervention study and declined participation. Thus, the assumption that participants will personally benefit from participating may not hold true for everyone and it is critical that the outcomes are personally meaningful to the individual.

Practically, it will be important for clinicians to help patients discern which benefits- whether physical, mental, psycho-social or emotional etc.- are most personally valuable to help identify the characteristics of a useful exercise program for that person. For example, for someone who values the sense of control associated with exercise, it may be important to prescribe highly customized exercise that accounts for their physical strengths and limitations. Conversely, for someone who derives the greatest value from the social engagement and camaraderie, it might be less important to customize the physical demands of their regimen and more important to facilitate exercise in a positive environment with their peers, friends or family.

Given the diverse needs, experiences and values of different people with ALS, standardized intervention studies and generic exercise prescription are not appropriate or useful for different people with ALS. Future exercise interventions should be designed to be customizable, accessible and personally valuable for different individuals living with ALS.

5.4.5 Limitations

The chosen methodology and research focus illuminated certain aspects of the lived experience for people with ALS while undoubtedly neglecting others. The findings presented herein are inherently biased given the participants' specific identities, circumstances, priorities, beliefs and symptomatology. Additionally, responses given during the interview process may have been influenced by the interviewer's status as a young, healthy researcher in the field of exercise physiology. The findings represent one set of interpretations that is by no means exhaustive or universal and the opinions and experiences expressed by the seven individuals living in the same geographic area may not be representative of other people experiencing ALS.

5.5 Conclusion

The purpose of this study was to explore what it is like to live with ALS and what is important about that experience for how people think about and engage with exercise. The findings can be used to informed the design of future exercise interventions that are more sensitive to the individuality of people living with ALS. The overarching finding is that negotiating decisions related to exercise within a progressively uncertain body is a complex and highly individual experience. While the diagnosis of ALS distinguishes certain physical bodies from others, the bodies that share this label can be tremendously different. Research designs and exercise protocols that rely on homogeneous subjects are poorly equipped to accommodate the individual needs of people with ALS. Therefore, both leisure-time and formal, structured exercise opportunities designed for people with ALS should employ a customizable and modifiable approach. Finally, numerous barriers were identified ranging from the psychological (e.g. minimal self-identified value in exercise) to the physical (e.g. lacking transportation to an exercise facility) which may serve as future targets for intervention to help facilitate increased participation in physical activity for people with ALS.

5.6 References

Berg, K. E., & Latin, R. W. (2008). *Essentials of research methods in health, physical education, exercise science, and recreation*. Lippincott Williams & Wilkins.

Braun, V., & Clarke, V. (2006). Using thematic analysis in psychology. *Qualitative research in psychology,* 3(2), 77-101

Braun, V., Clarke, V., & Weate, P. (2017). Using thematic analysis in sport and exercise research. In B. Smith & A. C. Sparkes (Eds.), *Routledge handbook of qualitative research in sport and exercise* (pp. 191-205). New York: Routledge.

Brott, T., Hocking, C., & Paddy, A. (2007). Occupational Disruption : Living with Motor Neurone Disease. *British Journal of Occupational Therapy*, *70*(January), 24–31.

Brown, J., & Addington-Hall, J. (2008). How people with motor neurone disease talk about living with their illness: A narrative study. *Journal of Advanced Nursing*, *62*(2), 200–208. https://doi.org/10.1111/j.1365-2648.2007.04588.x

Charmaz, K. (1991). *Good Days, Bad Days: the self in chronic illness and time*. New Brunswick, New Jersey: Rutgers University Press.

Dal Bello-Haas, V., Florence, J., Kloos, A., Scheibecker, J., Lopate, G., Hayes, S., … Mitsumoto, H. (2007). A randomized controlled trial of resistence exercise in individuals with ALS. *Neurology*, *68*, 2003–2007.

Dal Bello-haas, V., Florence, J. M., & Krivickas, L. S. (2013). Therapeutic exercise for people with amyotrophic lateral sclerosis or motor neuron disease (Review) Therapeutic exercise for people with amyotrophic lateral sclerosis or motor neuron disease, (4), 2–4. https://doi.org/10.1002/14651858.CD005229.pub2.Copyright

Dodd, K. J., Taylor, N. F., Denisenko, S., & Prasad, D. (2006). A qualitative analysis of a progressive resistance exercise programme for people with multiple sclerosis. *Disabil Rehabil*, *28*(18), 1127–1134. https://doi.org/10.1080/09638280500531842

Drory, V. E., Goltsman, E., Reznik, J. G., Mosek, a, & Korczyn, a D. (2001). The value of muscle exercise in patients with amyotrophic lateral sclerosis. *Journal of the Neurological Sciences*, *191*(1–2), 133–137. https://doi.org/10.1016/S0022-510X(01)00610-4

Elfhag, K., & Rössner, S. (2005). Who succeeds in maintaining weight loss? A conceptual review of factors associated with weight loss maintenance and weight regain. *Obesity Reviews : An Official Journal of the International Association for the Study of Obesity*, *6*(1), 67–85. https://doi.org/10.1111/j.1467-789X.2005.00170.x

Elsworth, C., Dawes, H., Sackley, C., Soundy, A., Howells, K., Wade, D., … Izadi, H. (2009). A study of perceived facilitators to physical activity in neurological conditions. *International Journal of Therapy and Rehabilitation*, *16*(1), 17–24. https://doi.org/10.12968/ijtr.2009.16.1.37936

Foley, G., Mahony, P. O., & Hardiman, O. (2007). Perceptions of quality of life in people with ALS : Effects of coping and health care, (December 2006), 164–169. https://doi.org/10.1080/17482960601164532

Horton, S., MacDonald, D. J., Erickson, K., & Dionigi, R. A. (2015). A qualitative investigation of exercising with MS and the impact on the spousal relationship. *European Review Of Aging And Physical Activity: Official Journal Of The European Group For Research Into Elderly And Physical*

Activity, *12*, 3. https://doi.org/10.1186/s11556-015-0148-5

Hughes, R. A., Sinha, A., Higginson, I., Down, K., & Leigh, N. P. (2005). Living with motor neurone disease: lives , experiences of services and suggestions for change. *Health and Social Care in the Community*, *13*(1), 64–74.

Kehn, M., & Kroll, T. (2009). Staying physically active after spinal cord injury: a qualitative exploration of barriers and facilitators to exercise participation. *BMC Public Health*, *9*(1), 168. https://doi.org/10.1186/1471-2458-9-168

Kiernan, M. C., Vucic, S., Cheah, B. C., Turner, M. R., Eisen, A., Hardiman, O., … Zoing, M. C. (2011). Amyotrophic lateral sclerosis. *The Lancet*, *377*(9769), 942–955. https://doi.org/10.1016/S0140-6736(10)61156-7

King, S. J., Duke, M. M., & O'Connor, B. A. (2009). Living with amyotrophic lateral sclerosis/motor neurone disease (ALS/MND): Decision-making about "ongoing change and adaptation." *Journal of Clinical Nursing*, *18*(5), 745–754. https://doi.org/10.1111/j.1365-2702.2008.02671.x

Lemoignan, J., & Ells, C. (2010). Amyotrophic lateral sclerosis and assisted ventilation : How patients decide. *Palliative and Supportive Care*, (8), 207–213. https://doi.org/10.1017/S1478951510000027

Levins, S. M., Redenbach, D. M., & Dyck, I. (2004). Individual and societal influences on participation in physical activity following spinal cord injury: a qualitative study. *Physical Therapy*, *84*(6).

Lunetta, C., Lizio, A., Sansone, V. A., Cellotto, N. M., Maestri, E., Bettinelli, M., … Corbo, M. (2016). Strictly monitored exercise programs reduce motor deterioration in ALS: preliminary results of a randomized controlled trial. *Journal of Neurology*, *263*(1), 52–60. https://doi.org/10.1007/s00415-015-7924-z

Ong, M. J., Guelfi, K. J., Hunter, T., Wallman, K. E., Fournier, P. A., & Newnham, J. P. (2009). Supervised home-based exercise may attenuate the decline of glucose tolerance in obese pregnant women. *Diabetes and Metabolism*, *35*(5), 418–421. https://doi.org/10.1016/j.diabet.2009.04.008

Phillips, M., Flemming, N., & Tsintzas, K. (2009). An exploratory study of physical activity and perceived barriers to exercise in ambulant people with neuromuscular disease compared with unaffected controls. *Clinical Rehabilitation*, *23*(8), 746–755. https://doi.org/10.1177/0269215509334838

Sundling, I., Ekman, S., Weinberg, J., & Klefbeck, B. (2017). Advances in Physiotherapy Patients ' with ALS and caregivers ' experiences of non-invasive home ventilation, *8196*(July). https://doi.org/10.1080/14038190701803351

van der Kolk, N. M., de Vries, N. M., Penko, A. L., van der Vlugt, M., Mulder, A. A., Post, B., … Bloem, B. R. (2017). A remotely supervised home-based aerobic exercise programme is feasible for patients with Parkinson's disease: results of a small randomised feasibility trial. *Journal of Neurology, Neurosurgery, and Psychiatry*, 12–15. https://doi.org/10.1136/jnnp-2017-315728

Vesey, S., Leslie, Æ. P., & Exley, Æ. C. (2008). A Pilot Study Exploring the Factors that Influence the Decision to have PEG Feeding in Patients with Progressive Conditions, 310–316. https://doi.org/10.1007/s00455-008-9149-0

Wigfield, A., & Eccles, J. S. (2000). Expectancy-Value Theory of Achievement Motivation. *Journal of Asynchronous Learning Network*, *6*(1), 68–81. https://doi.org/10.1006/ceps.1999.1015

Yuksel, P., & Yildirim, S. (2015). Theoretical Frameworks, Methods, and Procedures for Conducting Phenomenological Studies in Educational Settings. *Turkish Online Journal of Qualitative Inquiry*, *6*(January), 1–20.

Chapter 6

General Discussion

6.1 Summary of Key Findings

The present thesis has provided three important findings to the exercise and ALS literature. First, immense variability and individuality exists amongst people with ALS and their experiences with physical activity and exercise. Despite sharing the same diagnosis, individuals with ALS are characteristically different and should not be treated as a homogenous group, regarding exercise. Second, there are numerous physical, psychological and environmental barriers that appear to be common to individuals with ALS. These barriers may serve as targets for future interventions seeking to facilitate increased participation in physical activity and exercise. Third, contrary to the hypothesis of Chapter 3, exercise interventions should be customized to meet the individual physical and psychological needs of patients with ALS, generic exercise prescription is likely inappropriate.

6.2 Responding to the Call for Further Randomised Trials

A recent systematic review of randomised and quasi-randomised studies of exercise for people with ALS or MND arrived at the following conclusion:

> "The included studies were too small to determine to what extent strengthening exercise for people with ALS are beneficial, or whether exercise is harmful. There is a complete lack of randomised or quasi-randomised clinical trials examining aerobic exercise in this population. *More research is needed*." (Dal Bello-haas, Florence, & Krivickas, 2013)

This call for further research is echoed throughout the literature (Chen, Montes, & Mitsumoto, 2009; De Almeida et al., 2012; Lui & Byl, 2009) and the exercise trial described in Chapter 3 sought to respond by exploring the potential of sprint interval training as a useful modality. However, the study's inability to recruit sufficient participants called into question the feasibility, utility and suitability of randomised and quasi-randomised trials, and standardized exercise programs for people with ALS. The collective findings of Chapters 3 and 5 suggest that randomised trials, as previously designed, are poorly suited for examining the value of exercise for people with ALS. The following section will address some of the limitations of the RCT approach and suggest considerations for future exercise interventions in ALS.

Exercise intervention trials typically assume that there is widespread benefit of generic exercise prescription. Positive group mean responses are used to support claims about the usefulness of training protocol X for group Y, yet the individual responses within that group mean can be highly varied (Kohrt et al., 1991). The same standardized and supervised training has been shown to elicit positive, negative and non-response across a group of characteristically homogenous participants (Bonafiglia et al., 2016; Bouchard & Rankinen, 2001). ALS introduces an additional complexity in that individuals are not characteristically similar from disease diagnosis. Despite variance in age, anatomical site of onset, physical weakness and progression rate some study designs fail to acknowledge and account for that variance by using standardized interventions. Future intervention research could better accommodate people with ALS by utilizing individualized exercise interventions and outcome assessment, perhaps offered by a knowledgeable physiotherapist. While individualized exercise would certainly introduce more variability of intervention prescription, it would likely allow more people with ALS to participate and potentially benefit from regular exercise.

Further, there are inherent limitations of producing and interpreting high quality quantitative data given the variability of the subject group and the proposed individualized interventions. The research outcomes should be valuable to individual patients and to clinicians forming evidence-based exercise recommendations which likely requires a step away from quantitative measures like VO_2 peak, strength and function and the adoption of valuable subjective measures like quality of life questionnaires or a mixed-methods approach involving qualitative interviews of participant experience.

It is important to examine the value of the research intervention from the perspective of patients with ALS, which is different from the point of view of researchers. While quantitative researchers typically benefit from delineating relationships between and underlying mechanisms of intervention X and population Y, people with ALS are better served by research that demonstrates the general safety and usefulness of 'exercise' in the broadest sense. Certainly, future clinicians and health care professionals working with patients with ALS would benefit from identifying specific characteristics of interventions that are beneficial, however this information is not likely accessible through standardized exercise prescription and classic RCTs. Highly detailed and well-documented individualized interventions could lead to the development of a practical resource outlining useful, customizable exercise programs for people with ALS.

In place of a call for further randomised and quasi-randomised trials, the present thesis reveals the need for future research and exercise programs to appropriately accommodate the individual differences and complexities inherent to ALS. Much can be done beyond RCTs to support individuals with ALS in attaining the potential benefits of exercise.

6.3 Strengths

Alongside a very strong research team of both academic and clinical investigators, an attempt was made to conduct a well-designed intervention trial (Chapter 3). The real strength of this thesis however, is found in the response to the failure of Chapter 3. Rather than selecting a new topic that could be examined using familiar methods within the Queen's Muscle Physiology Lab, the primary investigator adopted a different research approach that has shed new light on the relationship between ALS and physical activity from the perspective of those living with ALS. Because of the research team's flexibility and tenacity in wanting to understand the answer to the original research questions, the secondary study resulted in novel, unique and important insight into the potential beneficial roles for exercise in the lives of ALS patients. The exploration of the research question from physiological, clinical and personal perspectives yielded important results with clinical implications and could shape much future work for ALS and exercise.

6.4 Limitations

Given time constraints for the completion of this thesis, data collection for Chapter 5 was stopped after seven participants were interviewed. There are undoubtedly views belonging to other individuals with ALS that are missing from the study described in Chapter 5. As well, most of the interviews were conducted in clinic during a period between consultations with different health care professionals (HCPs). At times interviewees expressed feeling tired from the numerous consultations and an eagerness to meet with the next HCP which may have limited the depth of insight expressed in the interview. Lastly, individuals with dysarthria experienced barriers to participating in an oral interview and despite offering written and typed options, producing detailed written responses involved considerable effort and deterred participation. Instead, one dysarthric participant chose to be represented by her spouse and corroborate his accounts of her life by nodding or shaking her head. Although this method generated valuable data, it should be acknowledged that the data did not represent the patient's primary experiences, but those interpreted by another person.

6.5 Future Directions

This research project underlined the integral role of end-users (people for which interventions are designed, e.g. people with ALS) in the development of knowledge and interventions designed for their benefit. Integrated knowledge translation (IKT) offers a useful approach where research is designed as a collaborative venture shared between researchers and knowledge/end users (Bowen & Graham, 2013). By involving the appropriate stakeholders from the very beginning, research findings are more likely to be useful for the production, dissemination and implementation of resulting knowledge. Future work in the area of ALS and exercise would greatly benefit from an IKT approach whereby interventions are explored, researched and designed alongside individuals with ALS who possess very important expert knowledge and hold a large stake in the success of future interventions.

Throughout the interviews described in Chapter 5, participants suggested that it would be useful to co-produce an 'Exercise & ALS Handbook' to empower individual patients to negotiate their own engagement in exercise. Under advisement of the appropriate stakeholders, this knowledge translation tool could outline current evidence, exercise regimen options including various modifications to account for differences in physical capabilities, accessible facilities and resources for accessing personal support. In addition to supporting patients and their families directly, the resource would be useful for other healthcare professionals involved in the patient's care like physiotherapists, occupational therapists and personal support workers that may be unfamiliar with the role of exercise for people with ALS.

Along with the handbook, another participant suggested that patients could be offered an invitation to connect with other people living with ALS through e-mail or an existing social network. Online forums have the potential to be more accessible than the monthly meetings organized by ALS Canada and held at a center in the community. A social hub may allow patients to share their experiences with exercise and life in general that may be useful and informative to others living with the disease.

Finally, several participants suggested that home exercise visits would reduce many of the barriers they currently experience with regards to regular exercise. To support those who experience substantial environmental barriers to leaving their home it was suggested that future programs involve home-visits and existing programs could be modified mediate this identified need.

6.6 MSc. Research Experience

Over the past two years as a graduate student I was afforded the quintessential learning opportunity to try, fail, learn and grow (and repeat indefinitely). Through this iterative process of failing and growing, I had the opportunity to explore my research topic from a multitude of viewpoints. From a physiological perspective, I learned what is and is not known about the etiology, pathophysiology and mechanisms of disease. From a clinical standpoint, I observed clinician-patient interactions and became familiar with the approach to symptom management. Finally, from a personal perspective, I had the privilege of listening to the stories of people living with the disease. Each of these valuable opportunities allowed me to develop a unique understanding of ALS, exercise and research more generally.

Beyond the knowledge gained, this experience led me to develop a stronger appreciation for qualitative methods and a better understanding of different paradigms valuable for framing different research questions. I am grateful for the opportunity to develop practical interviewing skills, writing skills and above all else, enriched critical thinking skills which will all serve me well in future research endeavours and my future practice as a physiotherapist.

6.7 Conclusion

ALS is an inherently variable and complex neuromuscular disease experienced differently by each person. Future exercise interventions must be customized to appropriately accommodate the specific needs of individual patients and greater efforts are needed to address the physical, psychological and environmental barriers that impair exercise engagement.

6.8 References

Bonafiglia, J. T., Rotundo, M. P., Whittall, J. P., Scribbans, T. D., Graham, R. B., & Gurd, B. J. (2016). Inter-individual variability in the adaptive responses to endurance and sprint interval training: A randomized crossover study. *PLoS ONE*, *11*(12), 1–15. https://doi.org/10.1371/journal.pone.0167790

Bouchard, C., & Rankinen, T. (2001). Individual differences in response to regular physical activity. *Medicine and Science in Sports and Exercise*, *33*(6).

Bowen, S., & Graham, I. D. (2013). Integrated knowledge translation. *Knowledge translation in health care: Moving from evidence to practice*, 14-23.

Chen, A., Montes, J., & Mitsumoto, H. (2009). The Role of Exercise in Amyotrophic Lateral Sclerosis. *Phys Med Rehabil Clin N Am*, *19*, 545–557.

Dal Bello-haas, V., Florence, J. M., & Krivickas, L. S. (2013). Therapeutic exercise for people with amyotrophic lateral sclerosis or motor neuron disease (Review) Therapeutic exercise for people with amyotrophic lateral sclerosis or motor neuron disease, (4), 2–4. https://doi.org/10.1002/14651858.CD005229.pub2.Copyright

De Almeida, J. P. L., Silvestre, R., Pinto, A. C., & De Carvalho, M. (2012). Exercise and amyotrophic lateral sclerosis. *Neurological Sciences*, *33*(1), 9–15. https://doi.org/10.1007/s10072-011-0921-9

Kohrt, W. M., Malley, M. T., Coggan, A. R., Spina, R. J., Ogawa, T., Ehsani, A. A., … Hol-L, J. O. (1991). Effects of gender, age, and fitness level on response of VO2max to training in 60-71 yr olds. *Journal of Applied Physiology*, *71*(5), 2004–2011.

Lui, A. J., & Byl, N. N. (2009). A systematic review of the effect of moderate intensity exercise on function and disease progression in amyotrophic lateral sclerosis. *Journal of Neurologic Physical Therapy : JNPT*, *33*(June), 68–87. https://doi.org/10.1097/NPT.0b013e31819912d0

Sisson, S. B., Katzmarzyk, P. T., Earnest, C. P., Blair, S. N., & Church, T. S. (2010). Volume of Exercise and Fitness Non-Response in Sedentary, Post-Menopausal Women. *Biomedical Research*, *41*(3), 539–545. https://doi.org/10.1249/MSS.0b013e3181896c4e.Volume

Appendix A:

Research Ethics Board- Letter of Informed Consent

Department of Neurology
School of Medicine
Queen's University
Kingston, Ontario, Canada, K7L 2V7

Consent to Volunteer for Participation in a Study

TITLE: Effect of exercise rehabilitation in patient with amyotrophic lateral sclerosis (ALS)

PRINCIPAL INVESTIGATOR: Sean Taylor, MD

Department of Neurology
School of Medicine
Queen's University
Kingston, Ontario, K7L 2V7
613-549-6666 ext. 3263

You are being invited to participate in a study examining the effects of an exercise training program on nerve and muscle health in patients with amyotrophic lateral sclerosis (ALS). You have been invited to participate in this study because you are an adult (18-80 years of age) who has been diagnosed with ALS by a medical doctor, or an adult 50-75 years of age with no history of neuromuscular disease. The following letter is intended to provide you with the details you should be aware of prior to your consent as a participant in this study. Please read the following information carefully and feel free to ask any question that you may have.

BACKGROUND INFORMATION

Previous studies have shown that patients with amyotrophic lateral sclerosis (ALS) who participate in exercise training may slow the development of ALS symptoms and they may feel improvements in physical fitness relative to ALS patients who do not engage in exercise. Additionally, exercise has been shown to be safe for patients with ALS. Studies investigating exercise and ALS previously have used exercise training of long duration at moderate intensities (similar to jogging at a steady rate for half an hour). It is not known how exercise training using short bursts and higher intensity exercise (also called interval training) may affect patients with ALS. In healthy active populations interval training is a safe, potent, time effective stimuli for improving muscle health and exercise capacity. We believe this type of exercise may be particularly beneficial for patients with ALS as it may provide a stronger stimulus to the neuromuscular system compared to continuous moderate intensity exercise. This study will examine how interval training may improve physical fitness and neuromuscular health of patients with ALS. Also, this study will investigate some of the changes that occur within the neuromuscular system that is leading to any improvements. Finally, we will also ask you a series of questions designed to increase our understanding of how much you enjoy participating in exercise training and if you would be willing to continue engaging in exercise on your own.

You will not be able to participate in the study if you have been diagnosed previously with any respiratory, cardiovascular (eg. high blood pressure, heart conditions), metabolic (eg. diabetes), neurological or musculoskeletal disease other than ALS; or you respond to the exercise protocol in an irregular manner (i.e. chest pains, dizziness, shortness of breath, excessive awareness of breathing)

EXPLANATION OF PROCEDURES

Participation

Participation in the study is voluntary. You may refuse to participate or withdraw from the study at any time. Withdrawing from the study will not in anyway affect your medical treatment or follow-up.

Should you choose to participate you will take part in experimental procedures outlined below. These include exercise tests, physiological tests, and an exercise training protocol. The investigator will explain to you, in detail how each of these procedures will be conducted in the study in which you have agreed to participate.

In-depth interview:

Following a regular clinical visit with Dr. Taylor, you will be invited to participate in a 45-minute interview about your experiences with and attitudes toward exercise before and after symptom onset. The interview will be recorded and your response to each individual question is completely voluntary. All responses will be kept anonymous and will be used to help identify areas of improvement for exercise prescription and adherence.

Exercise tests:

During each of the exercise tests you will be required to wear a nose-clip (to prevent you from breathing through your nose) and a rubber mouthpiece (similar to breathing through a snorkel or diving mask). This will enable us to measure the volume of air that you breathe in and out, and measure the gas concentration in that air. You may experience some initial discomfort from wearing the nose-clip and mouthpiece. You will also be required to wear a heart rate monitor around your chest during all tests. You will be asked to perform each of these tests on one occasion before and one occasion following exercise training.

> **Incremental exercise test:** This test is performed on either a stationary bike or a treadmill and is designed to measure your fitness level. During this test the intensity of exercise increases gradually until you are physically unable to continue exercising because the intensity is either too high or too uncomfortable. The test will begin with the exercise intensity being very light and easy (very little resistance). After a few minutes the exercise intensity will gradually and continuously increase until you are unable to continue because

of fatigue, or until you wish to stop.

Low-intensity exercise test: This test is performed on a cycle ergometer (a stationary bike) or a treadmill, and is designed to measure heart rate and your ability to burn fat during exercise. This test will last for approximately 30 minutes and will involve riding or jogging at a low-intensity (slow bike ride or light jog).

Exercise test of maximal power: This test is performed on a stationary bike and is designed to measure your ability to generate high levels of power during exercise. This test will involve either all out cycling and will take between 30 and 50 seconds.

Functional Ability and Well-being Questionnaire: This questionnaire is designed to assess your functional ability to perform activities of daily living (e.g. walking, eating, communicating with others). This questionnaire is part of the usual standard of care for patients with ALS and will take approximately 30 minutes to complete.

Psychological Questionnaires:

Following a regular clinical visit with Dr. Taylor you will be invited to respond to a questionnaire asking about your experiences with and attitudes toward exercise before and after diagnosis with ALS. Your response to each question is completely voluntary and all responses will be kept completely confidential. It is expected that this questionnaire will take less than 20 minutes to complete.

On the first visit, prior to the VO_2peak test, you will be required to fill out a series of questionnaires designed to determine the amount of physical activity you regularly perform and to predict whether or not you will enjoy high intensity exercise. It is expected that these questionnaires will take less than 30 minutes to complete.

Prior to your first visit to the lab, you will complete a questionnaire designed to determine how fatigued you feel over the course of a typical day. On two separate lab visits you will then perform two different exercise protocols. Following each exercise session, you will be asked to fill out an electronic survey to evaluate your feelings toward the exercise protocol;

how well you tolerated the exercise and whether your daily fatigue was impacted by the exercise. It is expected that this questionnaire will take less than 10 minutes to complete.

In addition, during training sessions of this study you will be asked a series of questions designed to evaluate how you are feeling towards the exercise you are performing.

Finally, following the exercise protocol you will be asked to fill out a series of questionnaires designed to determine how much you enjoyed the exercise and how likely you are to partake in exercise in the future. These final questionnaires should also take less than 30 minutes to complete.

All results from these questionnaires will be keep private and will be recorded in an anonymous fashion (i.e. by subject number rather than by name).

Physiological tests:

Blood sample: Both before and following training you will be asked to have a small sample of blood taken by a qualified and experienced phlebotomist. You may experience some minor discomfort when this small blood sample is drawn from a vein in your arm. The blood sampling may be painful and minor bruising is possible following venous blood sampling but generally fades within a few days.

Arm and Leg Muscle Size Measurements:

Before and after your exercise-training program you will be asked to have your arm and leg lengths and girths measured using a tape measure. This will provide an estimation of the size of your limb muscles. We are interested to see if the size of your muscles changes after you have completed the exercise-training program.

Muscle Biopsy: Before and after your training program you will be invited to have small amounts of muscle removed from your thigh muscle (quadriceps muscle) by means of a needle biopsy. The muscle biopsies will be taken by a medical doctor or by an individual trained in the technique under the supervision of a medical doctor. While you are resting on a bed, an anesthetic will be applied locally to anesthetize the skin over your thigh muscle at the sites where the biopsies will be taken. A small incision (less than 1 cm each) will be made through your skin and into your muscle at points approximately midway between your hip and knee. Small samples of muscle will be taken from each incision. This procedure is referred to as a biopsy.

There may be some discomfort associated with the biopsy procedure (like someone pressing hard into your muscle) but you should experience no pain. Following the exercise there may be light bruising of the leg muscle but this will generally fade within a couple of days. There is also a slight risk of infection following a biopsy but proper sterilization of equipment and cleaning of the sampled area minimizes this risk. If the site of the muscle biopsy becomes more tender and redness and/or swelling develops in that area over the next five to seven days you should seek medical attention immediately. You should also report this change to the research person supervising your study as soon as possible. **Please refer to the Muscle Biopsy Information Sheet for more information regarding this procedure.**

Note: you may decline muscle biopsy and still participate in other components of the research project.

Electromyography (EMG): The nerve and muscle properties of up to six different muscle groups may be tested before your first exercise training session, and after your last exercise training session. The muscles that may be tested include:

1. paraspinal muscles (back muscles that keep you upright) at the level of your ribs.
2. dorsiflexors (muscles that lift your toes and ankle) on the front of your leg.
3. plantar flexors (muscles that point your toes and extend your ankle) on the back of your leg.
4. knee extensors (muscles that straighten your knee) on the front of your thigh.
5. first dorsal interosseous (muscle that pulls your index finger toward your thumb) on your hand.
6. thenar muscles (the muscles that control the movement of your thumb) on your hand.

This aspect also may involve the administration of small electrical impulses to the skin at multiple locations (the ankle, knee, thigh, wrist, elbow and/or arm) to turn on one of the nerves that travels down your arm or leg. The nerve is initially turned on with low levels of stimulation, which you may not feel. The stimulation intensity is gradually increased until the best (largest) response is obtained. Responses from the nerve will be recorded from the skin over the muscle that the nerve supplies. Before each test, your skin will be cleansed and prepared using rubbing alcohol, and in some instances a mild abrasive strip of paper. Surface recording electrodes, which are small disposable adhesive pads, will be applied to the skin overlying the muscle we are recording from. This test will take approximately 30 minutes in total. We will be obtaining information from this test to examine the speed and quality with which your nerve conducts the electrical activity to your muscles in response to electrical stimulation.

You may also be asked to participate in intramuscular EMG tests of the same 6 muscles listed above. Intramuscular EMG requires brief (1-2 seconds) insertion of a small diameter needle into the muscle. The penetration of the skin feels like a pinprick, similar to acupuncture, and requires no anesthetic or special preparation other than a thorough cleansing of the skin with alcohol. Following insertion, the needle may be left in the muscle for a few minutes while you perform a series of low intensity muscle contractions. Both the surface and intramuscular EMG tests outlined here are often included in routine assessments by medical doctors specializing in nerve and muscle health.

Lung Function Testing:

You may be asked to perform several brief tests that examine your lung function. These tests are sometimes referred to as spirometry and are commonly used in patients with ALS. These lung tests involve breathing in and out of a mouthpiece. These tests will assess how well your lungs work by measuring how much air you inhale, how much you exhale and how quickly you can exhale. We may ask you to perform these brief lung function tests once before the exercise training program has started, and once again after you have finished the exercise program.

Daily Physical Activity Monitor:

Throughout the exercise training protocol you may be asked to wear a small, light wristband device that measures your daily activity level. This device is similar in size and weight to a wristwatch or bracelet. We may ask you to wear this activity monitor to determine if your physical activity levels change in response to acute exercise and over the course of your exercise-training program.

Exercise Training:

Any exercise carries a slight risk of heart attack or may be uncomfortable if you are unfit or not used to exercise. The risk of a cardiac event (heart attack, dysrhythmias etc.) in a mixed subject population (healthy low risk and unhealthy high risk patients together) is approximately 6:10 000. Patients with ALS have been shown to be able to participate in exercise safely. There may be some minor discomfort during the exercise testing. You may experience increased awareness of breathing, muscle pain and/or fatigue, increased sweating, or a general feeling of fatigue or nausea, all of which are not unexpected consequences of exercise.

Sprint Interval Training: This protocol involves performing 20 second maximal efforts of either cycling or stepping up and down a single stair as quickly and safely as possible, followed by 2 minutes of rest. This interval will be repeated 3 times per session and repeated 3 times per week for 6 weeks. ALS patients will perform the stair stepping SIT at home while older adults will perform either recumbent cycling or stepping under supervision in the lab.

EXPECTED STUDY TIMELINE

Pre-Study Enrolment: Initial recruitment for study participation

Week 1: Day 1 – Initial neurologic, functional, and electromyographic (EMG) assessment (1.5 hours) Receive accelerometer, wear for 7 days.

Week 2: Day 1- Electronic survey to answer (5 minutes) Receive accelerometer, wear during waking hours for 7 days.

Week 3: Day 1- Exercise session (40 min) and electronic surveys to follow (20 minutes), wear accelerometer for 48 hours following lab visit.

Week 4: Day 1- Exercise session (30 min) and electronic surveys to follow (20 minutes), wear accelerometer for 48 hours following lab visit.

Week 5: (Baseline for training)
Day 1 – Blood, biopsy, 8 foot-up and go, VO_2 peak test (1.5 hours)
Completion of initial psychological and exercise questionnaires (0.5 hours)

Day 2- (only for healthy 50-75 year olds) Low-intensity treadmill walking test

Week 6-11: Days 1 – 3 Exercise training sessions (~15 minutes per session) ALS patients perform exercise at home.

Week 12: Day 1 – Completion of final psychological and exercise questionnaires (0.5 hours)
Final blood and muscle biopsy samples (0.5 hours)
Final 8 foot up-and-go test
Final recumbent bike exercise test (1 hour)
Day 2 – Final neurologic and electromyographic (EMG) assessment (1.5 hours) only for ALS patients. Healthy older adults return to the lab for final low-intensity treadmill walking test.

RISK OF INJURY

All exercise carries a small risk of personal injury. Should any such injury occur during your participation in this study you will be initially cared for by the study administrators, all of whom are certified in first-aid. Should further assistance be required you will be taken to the university health centre/hospital or emergency as required.

POTENTIAL BENEFITS OF PARTICIPATION

You will be offered an honorarium of $50.00 cash for your participation in the study. You may gain some improvements to your level of physical fitness following completion of the exercise-training program relative to patients with ALS who do not engage in exercise training. If the exercise protocol is shown to be beneficial, the exercise program will be offered to all study participants. The administration of the protocol after the study with be co-ordinated through your own physical therapist and physical rehabilitation care providers.

CONFIDENTIALITY

During the course of your participation in this study you will not be required to provide any personal information beyond your name and phone number (for study purposes only). All information obtained during the course of this study, including your name and fitness results, is strictly confidential and your anonymity will be protected at all times. Your information will be kept in locked files and will be available only to Dr. Sean Taylor and Dr. Brendon Gurd and those working under their direct supervision. Your identity will not be revealed in any description or publication.

By signing this consent form, you do not waive your legal rights nor release the investigator(s) and sponsors from their legal and professional responsibilities.

VOLUNTARY CONSENT

I have been given an opportunity to ask any questions concerning the procedures. All of my questions regarding the research project have been satisfactorily answered. I understand that my test results are considered confidential and will never be released in a form that is traceable to me. I do understand that I am free to deny consent if I so desire, and may withdraw from the study at any time without any effect on my academic or employment status.

Should I have any questions about the study, I know that I can contact Dr. Sean Taylor (613 549-6666, ext 3263) directly. If you have any concerns about your rights as a research participant please contact Dr. Albert Clark, Chair for the Queen's University Health Sciences & Affiliated Teaching Hospitals Research Ethics Board (1-844-535-2988). A copy of this consent form will be provided me for my records. My signature below means that I freely agreed to participate in this study.

____________________________________ _________________

Volunteer's Signature **Date**

STATEMENT OF INVESTIGATOR

I, or one of my colleagues, have carefully explained to the subject the nature of the above research study. I certify that, to the best of my knowledge, the subject understands clearly the nature of the study and demands, benefits, and risks involved to participants in this study.

____________________________________ _________________

Principal Investigator's Signature **Date**

Appendix B:

Research Ethics Board- Letter of Approval

QUEEN'S UNIVERSITY HEALTH SCIENCES & AFFILIATED TEACHING HOSPITALS
RESEARCH ETHICS BOARD (HSREB)

HSREB Initial Ethics Clearance

July 21, 2015

Dr. Sean Taylor
Division of Neurology
Department of Medicine
Kingston General Hospital

ROMEO/TRAQ: #6015210
Department Code: DMED-1783-15
Study Title: Effect of exercise rehabilitation in patients with amyotrophic lateral sclerosis (ALS)
Co-Investigators: Dr. B. Gurd, Dr. M. Allen
Review Type: Delegated
Date Ethics Clearance Issued: July 21, 2015
Ethics Clearance Expiry Date: July 21, 2016

Dear Dr. Taylor,

The Queen's University Health Sciences & Affiliated Teaching Hospitals Research Ethics Board (HSREB) has reviewed the application and granted ethics clearance for the documents listed below. Ethics clearance is granted until the expiration date noted above.

- Task Self Efficacy Scale
- Feeling Scale
- Borg Rating of Perceived Exertion
- Physical Activity Enjoyment Scale
- ALS Functional Rating Scale
- Reference List
- Muscle Biopsy Information Letter
- Information/Consent Form

Documents Acknowledged:

- CORE Certificate – Dr. M. Allen

Amendments: No deviations from, or changes to the protocol should be initiated without prior written clearance of an appropriate amendment from the HSREB, except when necessary to eliminate immediate hazard(s) to study participants or when the change(s) involves only administrative or logistical aspects of the trial.

Renewals: Prior to the expiration of your ethics clearance you will be reminded to submit your renewal report through ROMEO. Any lapses in ethical clearance will be documented on the renewal form.

Completion/Termination: The HSREB must be notified of the completion or termination of this study through the completion of a renewal report in ROMEO.

Reporting of Serious Adverse Events: Any unexpected serious adverse event occurring locally must be reported within 2 working days or earlier if required by the study sponsor. All other serious adverse events must be reported within 15 days after becoming aware of the information.

Reporting of Complaints: Any complaints made by participants or persons acting on behalf of participants must be reported to the Research Ethics Board within 7 days of becoming aware of the complaint. Note: All documents supplied to participants must have the contact information for the Research Ethics Board.

Investigators please note that if your trial is registered by the sponsor, you must take responsibility to ensure that the registration information is accurate and complete.

Yours sincerely,

Albert J. Clark

Chair, Health Sciences Research Ethics Board

The HSREB operates in compliance with, and is constituted in accordance with, the requirements of the TriCouncil Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2); the International Conference on Harmonisation Good Clinical Practice Consolidated Guideline (ICH GCP); Part C, Division 5 of the Food and Drug Regulations; Part 4 of the Natural Health Products Regulations; Part 3 of the Medical Devices Regulations, Canadian General Standards Board, and the provisions of the Ontario Personal Health Information Protection Act (PHIPA 2004) and its applicable regulations. The HSREB is qualified through the CTO REB Qualification Program and is registered with the U.S. Department of Health and Human Services (DHHS) Office for Human Research Protection (OHRP). Federalwide Assurance Number: FWA#:00004184, IRB#:00001173

HSREB members involved in the research project do not participate in the review, discussion or decision.

Appendix C:

Research Ethics Board- Amendment Approval

QUEEN'S UNIVERSITY HEALTH SCIENCES & AFFILIATED TEACHING HOSPITALS RESEARCH ETHICS BOARD (HSREB)

HSREB Amendment Acknowledgment/Ethics Clearance

January 30, 2017

Dr. Sean Taylor
Division of Neurology
Department of Medicine
Kingston General Hospital

ROMEO/TRAQ: #6015210
Department Code: DMED-1783-15
Study Title: Effect of exercise rehabilitation in patients with amyotrophic lateral sclerosis (ALS)
Review Type: Delegated
Date Ethics Clearance Issued: January 30, 2017

Dear Dr. Taylor,

The Queen's University Health Sciences & Affiliated Teaching Hospitals Research Ethics Board (HSREB) has reviewed the amendment application and granted ethics approval/acknowledgement for the documents listed below.

- Addition of interviews and questionnaires
- Addition of chart review – KGH, HDH, SMOL
- Addition of $50 honorarium
- Revised Information/Consent Form
- Interview Guide
- Questionnaire

Yours sincerely,

Albert F. Clark

Chair, Health Sciences Research Ethics Board

The HSREB operates in compliance with, and is constituted in accordance with, the requirements of the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2); the International Conference on Harmonisation Good Clinical Practice Consolidated Guideline (ICH GCP); Part C, Division 5 of the Food and Drug Regulations; Part 4 of the Natural Health Products Regulations; Part 3 of the Medical Devices Regulations, Canadian General Standards Board, and the provisions of the Ontario Personal Health Information Protection Act (PHIPA 2004) and its applicable regulations. The HSREB is qualified through the CTO REB Qualification Program and is registered with the U.S. Department of Health and Human Services (DHHS) Office for Human Research Protection (OHRP). Federalwide Assurance Number: FWA#:00004184, IRB#:00001173

HSREB members involved in the research project do not participate in the review, discussion or decision.

Appendix D:

ALSFRS-R

Georgetown University Hospital
MedStar Health

The Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS)

Overview:
The Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS) is an instrument for evaluating the functional status of patients with Amyotrophic Lateral Sclerosis. It can be used to monitor functional change in a patient over time.

Measures:

(1) speech

(2) salivation

(3) swallowing

(4) handwriting

(5) cutting food and handling utensils (with or without gastrostomy)

(6) dressing and hygiene

(7) turning in bed and adjusting bed clothes

(8) walking

(9) climbing stairs

(10) breathing

Measure	**Finding**	**Points**
Speech	Normal	4
	Detectable speech disturbance	3
	Intelligible with repeating	2
	Speech combined with nonvocal communications	1
	Loss of useful speech	0
Salivation	Normal	4
	Slight but definite excess of saliva in mouth; may have nighttime drooling	3

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Georgetown University Hospital
MedStar Health

	With gastrostomy; some help needed with closures and fasteners	2
	With gastrostomy; provides minimal assistance to caregiver	1
	With gastrostomy; unable to perform any aspect of task	0
Dressing and hygiene	Normal	4
	Independent and complete self-care with effort or decreased efficiency	3
	Intermittent assistance or substitute methods	2
	Needs attendant for self-care	1
	Total dependence	0
Turning in bed and adjusting bed clothes	Normal	4
	Somewhat slow and clumsy but no help needed	3
	Can turn alone or adjust sheets but with great difficulty	2
	Can initiate but not turn or adjust sheets alone	1
	Helpless	0
Walking	Normal	4
	Early ambulation difficulties	3
	Walks with assistance	2
	Nonambulatory functional movement only	1
	No purposeful leg movement	0
Climbing stairs	Normal	4
	Slow	3

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Georgetown University Hospital
MedStar Health

	Moderately excessive saliva; may have minimal drooling	2
	Marked excess of saliva with some drooling	1
	Marked drooling; requires constant tissue or handkerchief	0
Swallowing	Normal	4
	Early eating problems; occasional choking	3
	Dietary consistency changes	2
	Needs supplemental tube feedings	1
	Nothing by mouth (NPO); exclusively parenteral or enteral feeding	0
Handwriting	Normal	4
	Slow or sloppy; all words are legible	3
	Not all words are legible	2
	Able to grasp pen but unable to write	1
	Unable to grip pen	0
Cutting food and handling utensils	No gastrostomy/normal	4
	No gastrostomy; somewhat slow and clumsy but no help required	3
	No gastrostomy; can cut most foods although clumsy and slow; some help needed	2
	No gastrostomy; food must be cut by someone but can still feed slowly	1
	No gastrostomy; needs to be bed	0
	With gastrostomy; normal	4
	With gastrostomy; clumsy but able to perform with manipulations independently	3

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	Mild unsteadiness or fatigue	2
	Needs assistance	1
	Cannot do	0
Breathing	Normal	4
	Shortness of breath with minimal exertion (walking, talking etc.)	3
	Shortness of breath at rest	2
	Intermittent (e.g. nocturnal) ventilatory assistance required	1
	Ventilator dependent	0

ALSERS = SUM (points for all 10 measures)

Interpretation:
- minimum score: 0
- maximum score: 40
- The higher the score the more function is retained.

Performance:
- It shows close agreement with objective measures of muscle strength and pulmonary function.
- It shows good construct validity and is sensitive to change in the patient's condition.
- It shows test-retest reliability and is consistent.

References:

ALS CNTF Treatment Study (ACTS) Phase I-II Study Group. The Amyotrophic Lateral Sclerosis Functional Rating Scale. Assessment of activities of daily living in patients with Amyotrophic Lateral Sclerosis. Arch Neurol. 1996; 53: 141-147.

Cedarbaum JM Stambler N. Performance of the Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS) in multicenter clinical trials. J Neurological Sciences. 1997; 152 (Suppl 1): S1 – S9.

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Appendix E:

Fatigue Severity Scale

FATIGUE SEVERITY SCALE (FSS)

Date ______________________________ Name __________________________________

Please circle the number between 1 and 7 which you feel best fits the following statements. This refers to your usual way of life within the last week. 1 indicates “strongly disagree” and 7 indicates “strongly agree.”

Read and circle a number.	Strongly Disagree → Strongly Agree						
1. My motivation is lower when I am fatigued.	1	2	3	4	5	6	7
2. Exercise brings on my fatigue.	1	2	3	4	5	6	7
3. I am easily fatigued.	1	2	3	4	5	6	7
4. Fatigue interferes with my physical functioning.	1	2	3	4	5	6	7
5. Fatigue causes frequent problems for me.	1	2	3	4	5	6	7
6. My fatigue prevents sustained physical functioning.	1	2	3	4	5	6	7
7. Fatigue interferes with carrying out certain duties and responsibilities.	1	2	3	4	5	6	7
8. Fatigue is among my most disabling symptoms.	1	2	3	4	5	6	7
9. Fatigue interferes with my work, family, or social life.	1	2	3	4	5	6	7

<u>VISUAL ANALOGUE FATIGUE SCALE (VAFS)</u>

Please mark an “X” on the number line which describes your global fatigue with 0 being worst and 10 being normal.

0	1	2	3	4	5	6	7	8	9	10

Appendix F:
Interview Guide

Draft Interview Guide

Living and Exercising with ALS

Researcher: Laura Sawula, 1Ljs3@queensu.ca

Introduction

Thank you for agreeing to chat with me today. As mentioned earlier, I'm a master's student at Queen's in the School of Kinesiology and Health Studies and I'm working with Dr. Taylor on this research project. We are interested in your thoughts on physical activity and exercise, and how they might inform physical type therapy for someone living with ALS. If it's okay with you, today we'll spend about 30 minutes chatting and I'm going to ask you some questions about your experiences being physically active. I have a recording device so that I can focus on our conversation and type it up later to look more closely at some of the ideas that come up. Everything you choose to share today is confidential and your identity will be anonymized, that means providing you with a pseudonym and changing identifiers like where you live and any people you might mention throughout the interview. I would be happy to provide you with a copy of the typed transcript for you to read over and make decisions about anything you'd prefer not to be used. In line with that, while we're chatting today if there is a question that you would prefer not to answer, please just say "I'd rather not answer that". Your participation is completely voluntary and you can choose to stop at any time.

Do you have any questions before we get started? If anything comes to mind while we're chatting- feel free to ask. Do you feel comfortable moving forward?

Interview Questions

1. Can you tell me about your home life?
2. What needs to happen when you have a medical appointment?
3. How do you like to spend your spare time?
4. Thinking back to a time before you felt symptoms related to ALS, what did physical activity look like in your life?
5. Can you describe any things that prevented you from doing ______ regularly?
6. What does physical activity look like in your life right now?
7. How do you feel after doing ________?
8. Can you tell me about any concerns or reasons you choose not to participate in certain activities?
9. What have you doctors shared with you about the usefulness of exercise?

10. How interested would you be in participating in an exercise program?
11. If there was an ideal time to start an exercise program, when do you think that would be and what would it look like?
12. What is your level of interest in participating in a exercise training study? And why
13. If we could test anything before and after training, what would be the most valuable to you?
14. Is there anything else on your mind that came up while we were chatting?

Appendix G:

Recruitment Hand-out

SKHS
School of Kinesiology and Health Studies

Queen's UNIVERSITY

We want to know what you think about exercise

Who? People with ALS and their loved ones/caregivers

What would I have to do?
Chat with Laura about your thoughts regarding exercise, this conversation will last about 30 minutes.

Why? Your responses will help us to better understand the value of physical activity for people living with ALS.

Are my responses anonymous?
Everything you share will be confidential, and your responses will remain anonymous.

Do I gain anything from participating?
You will contribute to the quality of future care for people and their families experiencing similar challenges. We are also offering a $50 honorarium in recognition of your time and contribution to the study.

If you are interested in participating, please phone Laura at **613-583-2611** or e-mail **1Ljs3@queensu.ca** to arrange a time for an interview. We would be happy to coordinate this with one of your existing clinical appointments.