



Mechanical Insufflation Exsufflation and Lung Volume Recruitment in Amyotrophic Lateral Sclerosis: a Prospective Study of the Prescription Process, the Outcomes and the Experience

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A thesis submitted to the School of Postgraduate Studies, Faculty of
Medicine and Health Sciences, Royal College of Surgeons in Ireland, in
fulfilment of the degree of Masters of Science by research

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October 2017

Candidate Thesis Declaration

I declare that this thesis, which I submit to RCSI for examination in consideration of the award of a higher degree by research, is my own personal effort. Where any of the content presented is the result of input or data from a related collaborative research programme this is duly acknowledged in the text such that it is possible to ascertain how much of the work is my own. I have not already obtained a degree in RCSI or elsewhere on the basis of this work. Furthermore, I took reasonable care to ensure that the work is original, and, to the best of my knowledge, does not breach copyright law, and has not been taken from other sources except where such work has been cited and acknowledged within the text.

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Table of Contents

List of Abbreviations	11
List of Figures	13
List of Tables	15
Summary	17
Acknowledgements	18
Funding Acknowledgements	20
Conference Presentations	20
Chapter 1: Introduction	21
1.1 Introduction	21
1.2 Background to the Thesis	21
1.3 Justification for the Thesis	22
1.4 Structure of the Thesis	23
Chapter 2: Respiratory Measurements, Physical Function and Airway Clearance Device Prescription over One Year in Amyotrophic Lateral Sclerosis: Literature Review	25
2.1 Introduction	25
2.2 Motor Neuron Disease	25
2.3 Amyotrophic Lateral Sclerosis	26
2.3.1 Clinical Features	26
2.3.2 Aetiology	27
2.3.3 Incidence and Life Time Risk	28
2.3.4 Prognosis and Survival	28
2.3.5 Diagnosis	29
2.3.5.1 El Escorial Criteria	31
2.3.6 Cognitive and Behavioural Changes	32
2.3.7 Management	33
2.3.7.1 Riluzole	33

2.3.7.2	Multidisciplinary Team Clinics	34
2.3.7.3	Nutrition	34
2.4	The Respiratory System	35
2.4.1	Normal Ventilation and Gas Exchange	35
2.4.2	Clinical Features of Respiratory Insufficiency	36
2.4.3	Diagnosis of Respiratory Insufficiency	37
2.4.4	Management of Respiratory Insufficiency	38
2.4.5	Non-Invasive Ventilation	38
2.4.6	Invasive Mechanical Ventilation	40
2.5	Cough	41
2.5.1	Cough Mechanism	41
2.5.2	Normal Cough Reflex	42
2.5.2.1	Cough in Amyotrophic Lateral Sclerosis	43
2.6	Respiratory Muscle Strength and Function, Cough Strength and Physical Function in Amyotrophic Lateral Sclerosis	43
2.7	Airway Clearance Devices	44
2.7.1	Mechanical Insufflation Exsufflation	45
2.7.2	Lung Volume Recruitment	46
2.7.3	Mechanical Insufflation Exsufflation and Lung Volume Recruitment Prescription	47
2.7.4	Evidence to support the use of Mechanical Insufflation Exsufflation and Lung Volume Recruitment	49
2.8	Research Question	56
2.9	Conclusion	58
Chapter 3: Respiratory Measurements, Physical Function and Airway Clearance Device Prescription over One Year in Amyotrophic Lateral Sclerosis: Development of Methodology		59
3.1	Introduction	59
3.2	Tests of Overall Respiratory Function	59

3.2.1	Vital Capacity	61
3.3	Tests of Respiratory Muscle Strength	64
3.3.1	Non-Volitional Tests of Respiratory Muscle Strength	64
3.3.1.1	Phrenic Nerve Stimulation	64
3.3.1.2	Abdominal Muscle Stimulation	64
3.3.2	Volitional Tests of Respiratory Muscle Strength	64
3.3.2.1	Maximal Static Inspiratory and Expiratory Pressure	64
3.3.2.2	Sniff Nasal Inspiratory pressure	65
3.4	Cough Tests	68
3.4.1	Peak Expiratory Flow	68
3.4.2	Cough Pressures	69
3.4.3	Peak Cough Flow	69
3.5	Physical Function	70
3.5.1	Amyotrophic Lateral Sclerosis Functional Rating Scale Revised	70
3.6	Outcome	71
3.7	Conclusion	72
Chapter 4: Respiratory Measurements, Physical Function and Airway Clearance Device Prescription over One Year in Amyotrophic Lateral Sclerosis: Methodology		73
4.1	Introduction	73
4.2	Study Design	73
4.3	Objectives and Hypotheses	73
4.4	Setting	74
4.5	Ethical Considerations	74
4.6	Sample Size	75
4.7	Participants	75
4.7.1	Identifying Participants	75
4.7.2	Inclusion and Exclusion Criteria	75

4.7.3	Recruitment	76
4.8	Assessments	76
4.8.1	Demographics	76
4.8.2	Respiratory Measures	76
4.8.2.1	Sniff Nasal Inspiratory Pressure	77
4.8.2.2	Slow Vital Capacity	78
4.8.2.3	Peak Cough Flow	80
4.8.3	Physical Function	80
4.8.3.1	Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised	80
4.8.4	Outcome	81
4.9	Prescription	81
4.10	Statistical Methods	82
4.11	Conclusion	83
Chapter 5: Respiratory Measurements, Physical Function and Airway Clearance Device Prescription over One Year in Amyotrophic Lateral Sclerosis: Results		84
5.1	Introduction	84
5.2	Participants	85
5.2.1	Excluded Participants	85
5.3	Missing Data	87
5.4	Description of Study Group	87
5.5	Amyotrophic Lateral Sclerosis Characteristics	90
5.6	Baseline Measurements	91
5.6.1	Respiratory Muscle Strength and Function, Cough Strength and Physical Function	94
5.7	Mortality	99
5.8	Chest Infection Frequency and Antibiotic Use	99
5.9	Prescription	100

5.9.1	Frequency of M-IE and LVR prescription	100
5.9.2	Characteristics of Participants not prescribed M-IE and LVR	101
5.9.3	Characteristics of Participants at the Time of M-IE and LVR prescription	104
5.9.3.1	Differences between Participants Prescribed M-IE and LVR at the Time of M-IE and LVR Prescription	107
5.9.4	Respiratory Symptoms	109
5.9.5	Differences between Spinal and Bulbar ALS Participants at the Time of M-IE and LVR Prescription	111
5.9.6	Comparison of Characteristics of Participants Prescribed M-IE and LVR and Participants not Prescribed M-IE and LVR	113
5.9.7	Comparison of Chest Infection Frequency and Antibiotic Use of Participants prescribed and not prescribed M-IE and LVR	120
5.10	Conclusion	122
Chapter 6: Respiratory Measurements, Physical Function and Airway Clearance Device Prescription over One Year in Amyotrophic Lateral Sclerosis: Discussion		123
6.1	Introduction	123
6.2	Description of the study group	124
6.3	ALS Characteristics	124
6.4	Baseline Measurements	124
6.4.1	Respiratory Muscle Strength and Function, Cough Strength and Physical Function	127
6.5	Mortality	131
6.6	Chest Infection Frequency and Antibiotic Use	131
6.7	Prescription	133
6.7.1	Frequency of M-IE and LVR prescription	133
6.7.2	Characteristics of participants at the time of M-IE and LVR prescription	134

6.7.2.1	Differences between Participants Prescribed M-IE and LVR at the time of M-IE and LVR prescription	136
6.7.3	Differences between Spinal and Bulbar ALS Participants at the Time of M-IE and LVR Prescription	137
6.7.4	Comparison of Characteristics of Participants Prescribed M-IE and LVR and Participants not Prescribed M-IE and LVR	138
6.7.5	Comparison of Chest Infection Frequency and Antibiotic Use of Participants Prescribed and Not Prescribed M-IE and LVR	140
6.8	Limitations	140
6.9	Considerations for Future Research	142
Chapter 7: Respiratory Measurements, Physical Function and Airway Clearance Device Prescription over One Year in Amyotrophic Lateral Sclerosis: Conclusion		145
Chapter 8: Experience and Usability of Mechanical Insufflation Exsufflation and Lung Volume Recruitment in Amyotrophic Lateral Sclerosis		148
8.1	Introduction	148
8.2	M-IE and LVR Patient Experience	148
8.3	Research Question	151
8.4	Methodology	151
8.4.1	Study Design	151
8.4.2	Setting	151
8.4.3	Ethical Considerations	152
8.4.4	Sample Size	152
8.4.5	Participants	152
8.4.5.1	Recruitment	152
8.4.5.2	Instrument Development	152
8.4.5.3	Questionnaire Assessment	153
8.4.6	Statistical Analysis	153
8.5	Results	154

8.5.1	Introduction	154
8.5.2	Demographics	154
8.5.3	Level of Dependence	155
8.5.4	Ease of Use	156
8.5.5	Comfort	157
8.5.6	Confidence	157
8.5.7	Knowledge Leaving Clinic	158
8.5.8	Cleaning	159
8.5.9	Reported Adherence	159
8.5.10	The Self-Reported Effect of M-IE and LVR on Speech Volume	161
8.5.11	The Self-Reported Effect of M-IE and LVR on Cough Strength	163
8.5.12	The Self-Reported Effect of M-IE and LVR on Cough Strength During a Chest Infection	164
8.5.13	Participant Feedback	164
8.6	Discussion	165
8.7	Limitations	171
8.8	Recommendations	172
8.9	Conclusion	172
Chapter 9: Development of a Prototype to Measure Adherence to Lung Volume Recruitment		174
9.1	Introduction	174
9.2	Literature Review	174
9.3	Methodology	176
9.3.1	Study Design	176
9.3.2	Setting	176
9.3.3	Ethical Considerations	176
9.3.4	Study Personnel	176

9.3.5	LVR Adherence Prototype Construct	177
9.3.6	Prototype Trials	177
9.4	Statistical Methods	178
9.5	Results	178
9.6	Discussion	180
9.7	Limitations	181
9.8	Considerations for Future Research	181
9.9	Conclusion	182
Chapter 10:	Overview and Conclusions of the Thesis	183
10.1	Introduction	183
10.2	Overview of the Thesis	183
10.3	Limitations of the Thesis	184
10.4	Recommendations for Future Research	185
10.5	Conclusion	185
	References	186
	Appendices	204

List of Abbreviations

ACPRC	Association for Chartered Physiotherapists in Respiratory Care
ALS	Amyotrophic Lateral Sclerosis
ALSFRS-R	Amyotrophic Lateral Sclerosis Functional Rating Scale Revised
APCF	Assisted Peak Cough Flow
ATS/ERS	American Thoracic Society and European Respiratory Society
BTS	British Thoracic Society
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
ECCS	European Community for Coal and Steel
EFNS	European Federation of Neurological Societies
ENCALS	European Network for the Cure of ALS
FVC	Forced Vital Capacity
GP	General Practitioner
ICC	Intraclass Correlation Coefficient
IARS	Irish Association of Respiratory Scientists
kPa	Kilopascal
L/min	Litre per minute
LVR	Lung Volume Recruitment
MAC	Manually Assisted Cough
MDT	Multidisciplinary Team
Median Diff	Difference of Median
MIC	Maximum Insufflation Capacity
M-IE	Mechanical Insufflation Exsufflation
ml	millilitre
MND	Motor Neuron Disease

N	Number
NICE	National Institute for Health and Care Excellence
NMD	Neuromuscular Disease
NIV	Non-Invasive Ventilation
PCEF	Peak Cough Expiratory Flow
PCF	Peak Cough Flow
pCO ₂	Partial Pressure of Carbon Dioxide
PEG	Percutaneous Endoscopic Gastrostomy
Pes	Oesophageal Pressure during Maximal Sniffs
QOL	Quality of Life
REM	Rapid Eye Movement
RCT	Randomised Control Trial
SD	Standard Deviation
SNIP	Sniff Nasal Inspiratory Pressure
SOD1	Superoxide Dismutase type 1
SVC	Slow Vital Capacity
UPCF	Unassisted Peak Cough Flow
VC	Vital Capacity
WHO	World Health Organisation
95% CI diff	Confidence Interval of the difference between the two groups

List of Figures

Figure 1.1: Summary of the Thesis	24
Figure 2.1: Breathing Muscles	36
Figure 2.2: The Three Phases of a Cough	42
Figure 2.3: A M-IE Device	46
Figure 2.4: Screen of M-IE Depicting Two Positive Insufflations and a Negative Exsufflation	46
Figure 2.5: LVR Equipment.....	47
Figure 4.1: MicroRPM Respiratory Pressure Meter	77
Figure 4.2: MicroLab (36-ML3500- MK8, Sword Medical, Blanchardstown, Dublin 15).	78
Figure 4.3: A 3 Litre Calibrating Syringe	79
Figure 4.4: Wright Peak Flow Meter.....	80
Figure 5.1: Flow of Participants.....	86
Figure 5.2: First Symptoms Reported by Spinal Onset ALS Participants.....	90
Figure 5.3: Linear Mixed Model of SNIP Decline Over One Year	96
Figure 5.4: Linear Mixed Model of PCF Decline Over One Year.....	97
Figure 5.5: Linear Mixed Model of SVC Percent Predicted Decline Over One Year	97
Figure 5.6: Linear Mixed Model of ALSFRS-R Decline Over One Year	98
Figure 5.7: Flow Chart of the Prescription of Devices During Study Period	101
Figure 5.8: Flow Chart of the Prescription of Devices Before and During Study Period	101
Figure 5.9: Bar Graph of Subjective Respiratory Symptoms at Time of Prescription of M-IE and LVR.....	109
Figure 5.10: Bar Graph of Subjective Respiratory Symptoms at Time of Prescription for M-IE	110
Figure 5.11: Bar Graph of Subjective Respiratory Symptoms at Time of Prescription for LVR.....	110
Figure 8.1: Bar Chart of Ease of Use Stratified by Site of Onset.....	156
Figure 8.2: Bar Chart of Comfort Stratified by Site of Onset	157
Figure 8.3: Bar Chart of Confidence Stratified by Site of Onset	158
Figure 8.4: Self-Reported Adherence of M-IE and LVR Use.....	160
Figure 8.5: Self-reported Adherence Stratified by Site of Onset	161
Figure 8.6: Self-reported effect of M-IE and LVR on Speech Volume.....	162

Figure 8.7: Self-reported effect of M-IE and LVR on Speech Volume Stratified by Site of Onset	163
Figure 8.8: Self-Reported Effect of M-IE and LVR on Cough Strength Stratified by Site of Onset	164
Figure 9.1: Adapted Facemask and Attached LVR Adherence Prototype Electronic Software and Hardware.....	178
Figure 9.2: Complete LVR Adherence Prototype Electronic Software and Hardware	179

List of Tables

Table 2.1: Clinical Features and Median Survival of MND Patients (Phukan and Hardiman, 2009)	26
Table 2.2: Diagnostic Requirements for ALS (Brooks et al., 2000)	30
Table 2.3: The Revised El Escorial Research Diagnostic Criteria for ALS with the Awaji Electrodiagnostic Algorithm Included (Andersen et al., 2012)	32
Table 2.2.4 Proposed Criteria for Non-invasive Ventilation (Andersen et al., 2012).....	39
Table 3.1: Tests of Overall Respiratory Function, their Purposes, Advantages and Disadvantages	60
Table 3.2: Summary equations for vital capacity for adults aged 18-70 years (Quanger et al., 1993).....	62
Table 4.1: Subjective Symptoms at Prescription.....	82
Table 5.1: Missing Data	87
Table 5.2: Demographics of Participants	88
Table 5.3: Demographics Stratified into Bulbar and Spinal Onset ALS.....	89
Table 5.4: Baseline Measurements.....	91
Table 5.5: Male and Female Baseline Measurements	92
Table 5.6: Spinal and Bulbar Baseline Measurements	93
Table 5.7: Respiratory Measurements and ALSFRS-R Rates of Decline over the Study Period	95
Table 5.8: Self-report and GP Report Chest Infections and Percentage Agreement between the Two Methods	100
Table 5.9: Demographics of Participants Not Prescribed a Device.....	102
Table 5.10: Demographics of Spinal and Bulbar Participants Not Prescribed a Device	103
Table 5.11: Demographics of Participants Prescribed a Device	105
Table 5.12: Demographics of Spinal and Bulbar Participants Prescribed a Device	106
Table 5.13: Respiratory Measures and ALSFRS-R scores of Participants at the Time of M-IE or LVR Prescription	107
Table 5.14: Comparison of Respiratory Measurements and ALSFRS-R between M-IE and LVR Prescription	108
Table 5.15: Spinal and Bulbar Respiratory Measures, ALSFRS-R Score and Time since Diagnosis to Prescription	112

Table 5.16: Comparison of Demographics of Participants Prescribed and Not Prescribed a Device	114
Table 5.17: Comparison of Time from Diagnosis to Study of Participants Prescribed and Not Prescribed a Device	115
Table 5.18: The Average Values of SNIP, SVC percent predicted, PCF and ALSFRS-R for Participants Prescribed a Device Compared to Participants not Prescribed a Device	116
Table 5.19: The Average Values of SNIP, SVC percent predicted, PCF and ALSFRS-R for Participants Prescribed M-IE Compared to Participants not Prescribed a Device	117
Table 5.20: The Average Values of SNIP, SVC Percent Predicted, PCF and ALSFRS-R for Participants Prescribed LVR Compared to Participants not Prescribed a Device	118
Table 5.21: The Changes of SNIP, PCF, SVC Percent Predicted and ALSFRS-R over Time between Participants Prescribed a Device and not Prescribed a Device	119
Table 5.22: Comparison of Self-Reported Chest Infection Frequency and Antibiotic Use between a Device and No Device	121
Table 8.1: Likert Scale	153
Table 8.2: Demographics of Participants that Completed the Questionnaire	155
Table 8.3: Participant Feedback on M-IE and LVR Experience and Usability	165
Table 9.1: Tester Interventions	179

Summary

Introduction: Mechanical Insufflation Exsufflation (M-IE) and Lung Volume Recruitment (LVR) increase cough strength in Amyotrophic Lateral Sclerosis (ALS). Changes in respiratory measures, morbidity, physical function and outcomes; participant's characteristics prescribed a M-IE and LVR device and their experience with devices are unknown. Finally, LVR adherence is difficult to measure.

Aims/Objectives: The primary aim was to measure, respiratory measures, morbidity, physical function and outcome in an Irish ALS cohort. Secondary aims were to examine the characteristics of participants prescribed a device; to evaluate their experiences and to develop an electronic LVR adherence prototype.

Methods: A prospective longitudinal observational cohort study evaluated 108 participants over one year. Respiratory measures, physical function and outcomes were measured. Characteristics were assessed at device prescription. A questionnaire evaluated experience. An electronic LVR adherence prototype was developed.

Results: Participants (n=108), of mean age 62.05 ± 11.47 , were recruited. Sniff Nasal Inspiratory Pressure (SNIP), Slow Vital Capacity (SVC) percent predicted, Peak Cough Flow (PCF) and Amyotrophic Lateral Sclerosis Functional Rating Scale Revised (ALSFRS-R) declined significantly ($p < 0.001$) at a rate of $18.72 \text{ cmH}_2\text{O}$, 17.49%, 124.84L/min and 9.62 units per year respectively. One third reported a chest infection and 21 died. Participants prescribed a device had significantly lower average SNIP, SVC percent predicted, PCF and ALSFRS-R ($p < 0.001$); site of onset and time from diagnosis was not significantly different to participants not prescribed a device. Experience with devices was positive. A sensitive (97.2%) electronic LVR adherence prototype was developed.

Conclusion: This is the first study to quantify the rate of decline of SNIP, SVC and PCF in an Irish ALS cohort and PCF in a large ALS cohort. Device prescription is detailed. This study provides a point of reference for clinicians and future trials. The electronic LVR adherence prototype has potential to be developed for clinical trials.

Acknowledgements

I would like to thank a number of people who made this research possible:

I would first like to thank my supervisors Dr. Dara Meldrum and Dr. Deirdre Murray for all their kindness, support and guidance throughout this research study.

Professor Orla Hardiman for giving me this opportunity to complete this research.

All the study participants who generously gave their time. Despite the poor prognosis associated with Amyotrophic Lateral Sclerosis, the participants were always very willing and helpful to participate in this research.

The Motor Neuron Disease clinic team that helped me recruit all my participants.

Beaumont Physiotherapy Department, for their continued support and encouragement of research in the department.

Mark Heverin, who helped me gather data from the Amyotrophic Lateral Sclerosis register information and his in-depth knowledge of each individual patient attending the Motor Neuron Disease clinic.

Killian Haycock, electrical engineer for his collaboration on the adherence study.

Katy Tobin and James Rooney, for statistical advice and guidance.

Roisin Vance for her clinical work and support throughout this research.

Laura Anderson, Grace Corcoran, Aoife Gallagher, Fiona Kinsella, Niamh McConnell and Tess Tattersall for proof reading chapters.

My colleagues in Beaumont Physiotherapy Department for their motivation and kind words.

To my parents, for their continued support and encouragement with education throughout my life. I thank you for all your sacrifices over the years to educate all of us.

My son Arthur who kept me company while writing the thesis. Finally, to my Husband Mark for all his patience, support and help throughout the two years.

Funding Acknowledgements

I would like to thank Research Motor Neuron who funded the work contained in the thesis and 3U partnership for funding a component of the Adherence Device Study.

Conference Presentations

McConnell R., Murray D., Hardiman O., Meldrum D. (October, 2016)
Mechanical Insufflation Exsufflation and Breath Stacking. The Patient's Experience. Poster Presentation at The Irish Society of Chartered Physiotherapists Conference, Wexford, Ireland

McConnell R., Murray D., Hardiman O., Meldrum D. (December, 2016)
Mechanical Insufflation Exsufflation and Breath Stacking. The Patient's Experience. Oral Presentation at The Allied Health Professionals Forum, Motor Neuron Disease Conference, Dublin, Ireland

Chapter 1: Introduction

1.1 Introduction

The purpose of this thesis was to present novel research in the area of respiratory management of Amyotrophic Lateral Sclerosis (ALS), which aimed to assist clinical practice, provide a point of reference for future studies and supplement the existing knowledge base in ALS. This thesis presents three studies. The first is a prospective longitudinal cohort study that measured respiratory muscle strength, function and morbidity, cough strength and outcomes in the form of chest infection frequency, antibiotic use and death. Simultaneously, an observational study analysed Mechanical Insufflation-Exsufflation (M-IE) and Lung Volume Recruitment (LVR) prescription and participant characteristics at the time of M-IE and LVR prescription. The second study, a cross sectional design assessed the participants experience and usability with M-IE and LVR. Finally, an electronic LVR adherence device was developed and tested for sensitivity in the third study.

1.2 Background to the Thesis

Amyotrophic Lateral Sclerosis, a form of Motor Neuron Disease (MND) is a progressive neurodegenerative disease (Kiernan et al., 2011) with a short survival of between three and five years after symptom onset (Turner et al., 2003, Andersen et al., 2012, Phukan and Hardiman, 2009). Respiratory insufficiency is the number one cause of morbidity and mortality in ALS (Turner et al., 2003). Respiratory muscle weakness impedes the mechanics of the respiratory system. Lung volumes are reduced and ventilation perfusion mismatching occurs. Objective and subjective signs of respiratory hypoventilation such as early morning headaches, fatigue, dyspnoea and orthopnoea are caused by rising arterial carbon dioxide in the blood (Piper, 2010). In addition, cough strength is reduced with all three phases of cough affected (Hadjikoutis et al., 1999). The inhalation volumes during the inspiratory phase decrease secondary to diaphragm muscle weakness; the compression phase can be unachievable in severe bulbar dysfunction patients and expiratory muscle strength, responsible for the expiratory phase of cough also decreases. An impaired cough can be distressing for ALS patients and impair the ability to expectorate secretions (Hadjikoutis et al.,

2000). The inability to independently expectorate secretions has been quantified by cough strength measured by Peak Cough Flow (PCF). A value of 160L/min is the cough critical threshold (Bach and Saporito, 1996). An ineffective cough is considered when a PCF less than 160L/min is measured in NMD patients.

Mechanical Insufflation-Exsufflation and LVR are two cough augmentation devices that are recommended for the use in ALS and NMD patients (Bott et al., 2009, Miller et al., 2009a, O'Callaghan et al., 2014, NICE, 2016). M-IE is an electronic device that applies positive and negative pressures to an individual's airway. The positive insufflation pressure increases inhalation volumes and the negative pressure or exsufflation phase aids expiratory flow. LVR a second cough augmentation device is performed with a resuscitator bag that is fitted with a one-way valve and a mask or mouthpiece. Breaths are manually stacked to increase inhalation volumes and the one way valve assists poor glottis function to achieve maximum volumes.

1.3 Justification for the Thesis

Mechanical Insufflation Exsufflation and LVR are recommended in the treatment of ALS (Bott et al., 2009, NICE, 2016, O'Callaghan et al., 2014, Miller et al., 2009a). It is known that M-IE and LVR increase cough strength for short durations in ALS patients (Cleary et al., 2013, Senent et al., 2011). However, the long term changes in respiratory muscle strength, function and morbidity, cough strength and outcomes associated with M-IE and LVR are unknown. M-IE and LVR are also recommended in the treatment of ALS (Bott et al., 2009, NICE, 2016, O'Callaghan et al., 2014, Miller et al., 2009a). The clinical practices and participant characteristics at the time of prescription of M-IE and LVR in ALS have also not been described. The patient's experience and their analysis of M-IE and LVR usability in ALS are not documented. A method to accurately measure adherence of LVR would provide a valuable tool in a much needed Randomised Control Trial (RCT). This novel piece of research has the potential to facilitate clinical practices managing ALS patients and to supplement an existing knowledge base in ALS.

1.4 Structure of the Thesis

The thesis comprises of ten chapters. The first chapter outlines the background, justification and structure of the thesis. Chapter 2 provides an in-depth description of ALS and critiques the available literature of M-IE and LVR. In this chapter, gaps in the literature were identified. This included the limited long term evaluation of respiratory outcomes and physical function; the undetermined rate of change in respiratory muscle strength, function and morbidity and physical function after the implementation of M-IE and LVR in ALS; the lack of detail on the current practices of M-IE and LVR prescription in an Irish ALS population and the unknown characteristics of ALS participants prescribed M-IE and LVR. Chapter 3 evaluates outcome measures that could be employed within the one year prospective longitudinal study. This chapter then comprehensively details and justifies the outcome measures that were utilised. Chapter 4, the methods chapter follows the development of methodology and provides a complete description of the methods undertaken to complete the one year prospective longitudinal study. Chapter 5 states the results of this study. Chapter 6, the discussion chapter answers the questions that were identified in the literature review; explains the results to support these answers. Chapter 7 concludes and describes how these answers contribute to the literature of M-IE and LVR in ALS. A second study is described in Chapter 8. This chapter details the quantitative analysis of experience and usability of M-IE and LVR in ALS. Chapter 9 describes the third study. The development of an electronic LVR adherence prototype and its associated sensitivity and specificity is described. Chapter 10, the final chapter concludes the thesis and summarises the thesis findings and its contribution to literature. A summary of the structure of the thesis is described in Figure 1.1.

Chapter 1	<ul style="list-style-type: none"> • Introduction to the Thesis
Chapter 2	<ul style="list-style-type: none"> • A literature review that details the symptoms and medical management of ALS and critiques the available literature of M-IE and LVR in ALS
Chapter 3	<ul style="list-style-type: none"> • The available outcome measures for the prospective longitudinal and observational cohort study in ALS are analysed and the chosen outcome measures are justified
Chapter 4	<ul style="list-style-type: none"> • The methods to undertake the prospective longitudinal and observational cohort study are described
Chapter 5	<ul style="list-style-type: none"> • The results of the prospective longitudinal and observational cohort study are stated
Chapter 6	<ul style="list-style-type: none"> • The findings of the prospective longitudinal and observational cohort study are discussed
Chapter 7	<ul style="list-style-type: none"> • The conclusion of the prospective longitudinal and observational cohort study are discussed
Chapter 8	<ul style="list-style-type: none"> • A literature review, methodology, results, discussion and conclusion of the "Experience and Usability of M-IE and LVR in ALS" are presented
Chapter 9	<ul style="list-style-type: none"> • Development of a Prototype to Measure Adherence to LVR
Chapter 10	<ul style="list-style-type: none"> • Conclusions, implication and contribution of the thesis

ALS=Amyotrophic Lateral Sclerosis, M-IE= Mechanical Insufflation-Exsufflation, LVR=Lung Volume Recruitment

Figure 1.1: Summary of the Thesis

Chapter 2: Respiratory Measurements, Physical Function and Airway Clearance Device Prescription over One Year in Amyotrophic Lateral Sclerosis: Literature Review

2.1 Introduction

An in-depth review of the relevant literature pertaining to Amyotrophic Lateral Sclerosis (ALS), its clinical presentation, diagnosis, and medical and symptom management will be presented in this chapter. A critical review of the Mechanical Insufflation Exsufflation (M-IE) and Lung Volume Recruitment (LVR) literature will also be presented. Finally, the research study hypotheses and objectives will be outlined.

2.2 Motor Neuron Disease

Motor Neuron Disease (MND) is classified into four disease categories; ALS, Primary Lateral Sclerosis, Progressive Muscle Atrophy and Progressive Bulbar Palsy. The disease categories are distinguished by upper and lower motor neuron involvement. Table 2.1 outlines clinical features and median survival of patients in each category (Phukan and Hardiman, 2009). The research presented in this thesis focused on individuals with ALS.

**Table 2.1: Clinical Features and Median Survival of MND Patients
(Phukan and Hardiman, 2009)**

Disease	Clinical Features	Survival
Amyotrophic Lateral Sclerosis	Upper and lower motor neuron signs at multiple spinal levels	3–5 years
Primary Lateral Sclerosis	Upper motor neuron signs only	20 years or more
Progressive Muscle Atrophy	Lower motor neuron signs only	5 years. A proportion will survive 20 years or more
Progressive Bulbar Palsy	Speech and swallowing affected initially due to Lower motor neuron involvement of cranial nerve IX, X, XI	2–3 years

2.3 Amyotrophic Lateral Sclerosis

ALS is a fatal and progressive neurodegenerative disease involving motor neurones of the cerebral cortex, brainstem and spinal cord (Kiernan et al., 2011). Death typically occurs within three to five years of symptom onset but survival greater than 10 years can occur in 5% to 10% of patients (Turner et al., 2003, Andersen et al., 2012, Phukan and Hardiman, 2009).

2.3.1 Clinical Features

The onset of ALS is insidious and progressive. Upper and lower motor neuron involvement is the hallmark of ALS. Bulbar, thoracic and abdominal progressive muscle weakness occurs (Andersen et al., 2012). Initial symptoms can be ambiguous and include muscle twitching, muscle cramping, muscle weakness, dysphagia, dysarthria and sialorrhea (Phukan and Hardiman, 2009). Spinal onset ALS presents in 70%, bulbar onset in 25% and trunk or respiratory involvement in 5% of cases (Phukan and Hardiman, 2009, Körner et al., 2011).

Spinal onset ALS presents with muscle weakness, fasciculations, atrophy, deep tendon reflexes and spasticity. Initial symptoms of spinal onset ALS commence in the lower limbs more frequently than the upper limbs (Chio et al., 2002). Spread of symptoms occurs after initial site of onset, firstly to adjacent muscle regions and then to involve general skeletal muscles in the later stages of disease (Ravits et al., 2007, Körner et al., 2011). The frequency of all four limb involvement increases with progression of the disease (Traynor et al., 2000b).

Bulbar symptoms include dysphagia, dysarthria and sialorrhea (Phukan and Hardiman, 2009). Dysarthria is more commonly reported than dysphagia as an initial symptom in bulbar onset ALS (Traynor et al., 2000b). The incidence of bulbar onset ALS increases with advancing age (Chio et al., 2002, Traynor et al., 2000b).

Pseudobulbar symptoms are present in 50% of cases of ALS (Phukan and Hardiman, 2009). Other less common non-motor presentations include weight loss, frontal lobe type cognitive impairment, cramps and fasciculations with normal muscle power.

The mean age of onset is 58–63 years in sporadic cases and 43–52 years in familial cases (Haverkamp et al., 1995). The mean age at diagnosis has been reported as 63.7 years (Chio et al., 2002). Age of onset peaked at 75 to 79 years for both men and women in a United Kingdom study (Alonso et al., 2009).

ALS and also spinal onset ALS is more common in men than women (Alonso et al., 2009, Rooney et al., 2013, Logroscino et al., 2010). Spinal onset was present in 58.4%, bulbar onset in 36.5% and a general mixed presentation in 5.1% of Irish cases diagnosed between 1995–2010 (Rooney et al., 2013).

2.3.2 Aetiology

The mechanisms leading to cell death are unknown and the pathogenic processes are possibly multifactorial in ALS. Genetic risk factors have been identified and it is thought that at least six genes are linked to ALS (Shaw, 2005) including Superoxide Dismutase type 1 (SOD1) and C9orf72. The specific mechanism of SOD1 neurodegeneration is unknown (Hardiman and

Greenway, 2007) however, much research has been carried out on its mechanism indicating a complex interaction of numerous pathogenic actions (Takeuchi et al., 2002, Pasinelli et al., 2004). The C9orf72 gene has been identified in the Irish ALS population (Byrne et al., 2012). The characteristics of the C9orf72 gene are the presence of cognitive and behavioural changes (2.3.6), a lower age of onset, precise neuroimaging changes, reduced survival and a family history of neurodegeneration.

2.3.3 Incidence and Life Time Risk

The global incidence rate of ALS has been reported as 1.9 (Chio et al., 2013) and 1.75 per 100,000 population (Marin et al., 2016). The annual incidence rate of ALS in Europe is 2.16 per 100,000 person-years (Logroscino et al., 2010). In Ireland, 1,282 cases of ALS were diagnosed between 1995–2010, (Rooney et al., 2013). Incidence in Ireland is two per 100,000 population. In the UK, incidence has been reported as 3.1 per 100,000 person per year in women and 4.3 per 100,000 person per year in men (Alonso et al., 2009). At any one time, approximately 300 people live with ALS in Ireland. It is expected that the number of global cases of ALS will increase from 222,801 in 2015 to 376,674 in 2040. An ageing population is the main reason for this expected increase (Arthur et al., 2016).

The lifetime risk of developing MND including ALS is one in 472 for women and one in 350 for men (Alonso et al., 2009). The majority of cases are sporadic but familial cases have been reported from 5% to 23% (Traynor et al., 2000b, Andersen et al., 2012). There is currently no criteria for the definition of familial cases but it is considered if one or more first or second degree relatives is diagnosed with ALS (Byrne et al., 2011). The SOD1 gene accounts for 20% of familial cases. Other genes are associated with familial ALS such as the C9orf72 identified in Irish cases (Wijesekera and Leigh, 2009, Byrne et al., 2012).

2.3.4 Prognosis and Survival

The average survival for a person diagnosed with ALS is three years after symptom onset. Approximately 10% will have a slower progression of disease and will survive 10 years or more after symptom onset (Del Aguila et al., 2003, Turner et al., 2003, Andersen et al., 2012). Bulbar onset, older age

at onset and definite ALS El Escorial criteria at presentation are negative prognostic indicators (Chio et al., 2002, Turner et al., 2003). Speech, swallowing problems, weight loss, poor respiratory function, lower Amyotrophic Lateral Sclerosis Functional Rating Scale Revised (ALSFRS-R) score, frontal temporal dementia, and short duration from initial symptoms to time of diagnosis are also prognostic indicators of a shorter survival in ALS (NICE, 2016, Chio et al., 2009, Andersen et al., 2012). A better prognosis is associated with younger age at onset (Turner et al., 2003) and access to an ALS Multidisciplinary Team (MDT) clinic (Traynor et al., 2003, Chio et al., 2006).

An awareness of the prognosis of ALS is vital for patients and family members to plan and prepare for end of life. Patients should be informed of the expected prognosis if the diagnosis of ALS is suspected or confirmed, highlighting that survival can be unpredictable, with some patients living more than 10 years after diagnosis (NICE, 2016) (Andersen et al., 2012).

2.3.5 Diagnosis

There is no single diagnostic tool or biological marker that exists to confirm or exclude ALS. As a result, diagnosis can be difficult in combination with the highly variable clinical presentations. Diagnosis of ALS is based on clinical presentation of the presence of upper and lower motor neuron signs, progression of the disease and the absence of an alternative diagnosis (Phukan and Hardiman, 2009).

Delay in diagnosis occurs because of the highly variable clinical presentations. The time from symptom onset to diagnosis varies among studies and the timeframe has been documented as a median of eight (Traynor et al., 2000b), a mean of 11 (Chio et al., 2002) and a mean of 16 months (Galvin et al., 2015). Prior to a participant's first MDT clinic visit there was an average of four contacts with a healthcare provider and 4.8 investigations completed in an Irish population (Galvin et al., 2015)

Clinical criteria are used to diagnose ALS (Table 2.2). The European Federation of Neurological Societies (EFNS) task force recommend that all patients with a suspected case of ALS should have a diagnosis explored as early as possible. It is recommended that patients are referred to an

experienced neurologist for detailed clinical and paraclinical examinations. Some cases may require repetitive testing and additional investigations. The diagnosis should be reviewed if progression of the disease is not typical or atypical signs develop (Andersen et al., 2012).

Table 2.2: Diagnostic Requirements for ALS (Brooks et al., 2000)

The diagnosis of ALS requires the presence of (positive criteria):

Evidence of lower motor neuron degeneration by clinical, electrophysiological or neuropathologic examination

Evidence of upper motor neuron degeneration by clinical examination and

Progressive spread of symptoms or signs within a region or to other regions, as determined by history or examination

The diagnosis of ALS requires the absence of (diagnosis by exclusion):

Electrophysiological or pathological evidence of other disease processes that might explain the signs of lower motor neuron and/or upper motor neuron degeneration, and

Neuroimaging evidence of other disease processes that might explain the observed clinical and electrophysiological signs

The diagnosis of ALS is supported by:

Fasciculations in one or more regions

Neurogenic changes in EMG results

Normal motor and sensory nerve conduction

Absence of conduction block

Investigations to be undertaken include electrophysiology, neuroimaging and routine blood tests to exclude other conditions such as anatomical abnormalities, infections, myopathies and vascular disorders (Andersen et

al., 2012). Five to 8% of ALS cases can be misdiagnosed (Andersen et al., 2012) and misdiagnosis has been reported as 7.3% in an Irish study (Traynor et al., 2000a) of which half of cases are treatable (Davenport et al., 1996).

2.3.5.1 *El Escorial Criteria*

El Escorial criteria were created to form internationally accepted criteria for the diagnosis of ALS for the purpose of research (Brooks, 1994). The El Escorial criteria were revised in 2000 (Brooks et al., 2000) (Table 2.3). The El Escorial criteria have been validated (Chaudhuri et al., 1995) and are sensitive in early ALS diagnosis (Andersen et al., 2012). Categories of clinical diagnosis certainty on clinical criteria alone exist. This categorises ALS into different levels of certainty depending on the upper and lower motor neuron signs in the same topographical anatomic region in the brainstem, or the cervical thoracic, or lumbosacral spinal cord (Brooks et al., 2000).

Criticism of the El Escorial criteria exists. Research of phenotypes and prognostic indicators has expanded the knowledge of ALS and researchers consider the criteria to be restrictive (Agosta et al., 2015).

Table 2.3: The Revised El Escorial Research Diagnostic Criteria for ALS with the Awaji Electrodiagnostic Algorithm Included (Andersen et al., 2012)

Clinically definite ALS

Upper motor neuron and lower motor neuron clinical signs or electrophysiological evidence in three regions

Clinically definite ALS – laboratory supported

Upper motor neuron and/or lower motor neuron clinical signs in one region and the patient is a carrier of a pathogenic SOD1-gene mutation

Clinically probable ALS

Upper motor neuron and lower motor neuron clinical or electrophysiological evidence by lower motor neuron and upper motor neuron signs in two regions with some upper motor neuron signs rostral to the lower motor neuron signs

Clinically possible ALS

Upper motor neuron and lower motor neuron clinical or electrophysiological signs in one region only, or

Upper motor neuron signs in at least two regions, or

Upper motor neuron and lower motor neuron signs in two regions with no upper motor neuron signs rostral to lower motor neuron signs. Neuroimaging and laboratory studies have excluded other diagnoses.

2.3.6 Cognitive and Behavioural Changes

Neuropsychiatric and cognitive changes can be present in up to 50% of patients with ALS (Mioshi et al., 2014, Ringholz et al., 2005). Approximately 15% of patients with ALS will receive a diagnosis of ALS with frontal temporal dementia but the remainder who do not fit this criterion have significant cognitive and behavioural changes (Ringholz et al., 2005).

Frontotemporal dementia and executive dysfunction are negative prognostic

indicators in ALS (Elamin et al., 2011). Cognitive and behavioural symptoms can often precede motor symptoms (Mioshi et al., 2014). The most common symptom is apathy, reported in 60% (Grossman et al., 2007) followed by disinhibition (Lillo et al., 2011).

Caregiver burden can be increased as a result of these cognitive and behavioural changes. The factors that contribute to caregiver burden include level of disability, depression, low mood, anxiety and total distress (Burke et al., 2015). Caregiver burden does not influence survival (Burke et al., 2015) but further investigation of caregiver burden and appropriate support and education of caregivers is a priority for future research and service provision (Galvin et al., 2016).

Problems can be encountered managing ALS patients with frontotemporal dementia around adherence and medical decisions (Andersen et al., 2012). Improved understanding and education of cognitive and behavioural changes in ALS patients among healthcare professionals is important to increase the standard of care and management (Orsini et al., 2016, Andersen et al., 2012). In addition, early identification of cognitive and behavioural changes is important to help clinical care and to reduce caregiver burden (Mioshi et al., 2014).

2.3.7 Management

2.3.7.1 Riluzole

Riluzole (Rilutek) is a disease-modifying therapy for patients with ALS. It is recommended for the treatment of ALS and it should be prescribed by a specialist neurologist (NICE, 2001) for ALS patients as early as possible (Andersen et al., 2012). Clinical trials have demonstrated that 100mg per day of Riluzole improves survival for patients with ALS by two to three months (Miller et al., 2012).

It is the only medication available that can slow the course of ALS. It is hypothesised that the destruction of motor neurons is the result of excess stimulation of glutamate receptors, a neurotransmitter. Riluzole impedes the release of glutamate and protects cells from destruction (Distad et al., 2008).

2.3.7.2 Multidisciplinary Team Clinics

Specialist MDT clinics include physiotherapists, occupational therapists, speech and language therapists, dieticians, specialist nurses, psychologists, doctors, social workers, respiratory therapists and palliative care. Immediate referral to a specialised MDT clinic is recommended (Phukan and Hardiman, 2009, NICE, 2016).

Improved survival and enhanced Quality of Life (QOL) are associated with specialist ALS MDT clinics when compared with care in a general neurology clinic (Traynor et al., 2003, Chio et al., 2006). Access and use of a number of resources at one clinic visit may contribute to these positive outcomes. In addition, cost-effectiveness has also been associated with ALS MDT ALS care (Chio et al., 2006, Galvin et al., 2015, NICE, 2016) with a cost effectiveness of £26,672 per quality-adjusted life-year (Oliver, 2016).

2.3.7.3 Nutrition

Nutritional status is a prognostic factor for survival of ALS. Weight loss and low body mass index are negative prognostic indicators for survival of ALS (Desport et al., 1999). Weight loss occurs because of dysphagia but it can occur without dysphagia possibly because of higher energy expenditure secondary to muscle fasciculations, increased respiratory effort, hyper metabolism and reduced oral intake secondary to depression (Körner et al., 2013). Nutrition and feeding assessment should be performed regularly (NICE, 2016). Percutaneous Endoscopic Gastrostomy (PEG) can aid calorie, nutritional and hydration intake. PEG insertion is recommended to stabilise weight in ALS patients with impaired oral food intake (Miller et al., 2009b), however there is no evidence to support that PEG insertion prolongs life.

The aims of palliative care are to improve QOL and function, relieve symptoms and help patients and families make end-of-life decisions. Relief of symptoms can include management of pain, mood disorders, sialorrhea and dyspnoea and respiratory failure (Blackhall, 2012). Early access to palliative care services is recommended (Phukan and Hardiman, 2009). Advanced directives are discussed with the patient and family soon after diagnosis (Andersen et al., 2012, NICE, 2016).

2.4 The Respiratory System

Respiratory complications are the leading cause of death in ALS. Motor neuron involvement decreases respiratory muscle power, causing ventilation dysfunction and an ineffective cough, resulting in respiratory complications (Turner et al., 2003). Respiratory muscle function is a predictor of survival (Chio et al., 2002) and it is strongly and independently related to QOL in ALS patients (Bourke et al., 2001). It is important to understand normal and pathological mechanisms of ventilation and cough and their management to comprehend the respiratory complications present in ALS.

2.4.1 Normal Ventilation and Gas Exchange

Gas exchange is the primary function of the respiratory system. Oxygen enters and carbon dioxide is removed from the blood (Hough, 2013). A large surface area of alveoli and a thin membrane that separates alveoli and blood vessels allows rapid gas diffusion (Petersson and Glenny, 2014). Normal gas exchange also requires the mechanics of inspiratory and expiratory muscle function to generate adequate pressures and blood flows to facilitate air movement (Ward et al., 2010).

The diaphragm is the primary muscle active during quiet breathing. It contracts and increases the chest wall diameter to increase thoracic volume and decrease intrapleural pressure. The decrease in intrapleural pressure increases the pressure gradient between the intrapleural space and alveoli, causing the lungs to stretch and the alveoli to expand. A pressure gradient between the mouth and alveoli is created, resulting in a flow of air into the lungs. The lungs recoil without activation of the expiratory muscles (Ward et al., 2010).

The accessory inspiratory muscles are exercised during active breathing (Figure 2.1). They are scalene muscles, sternocleidomastoids and serratus anterior. The expiratory muscles, rectus abdominus, external and internal oblique are also activated. The contraction of the expiratory muscles increases the recoil speed and increases intra-abdominal pressure. Accessory inspiratory and expiratory muscles allow for larger inhalation volumes and higher intra-abdominal pressures, enabling efficient gas exchange during active breathing (Ward et al., 2010).

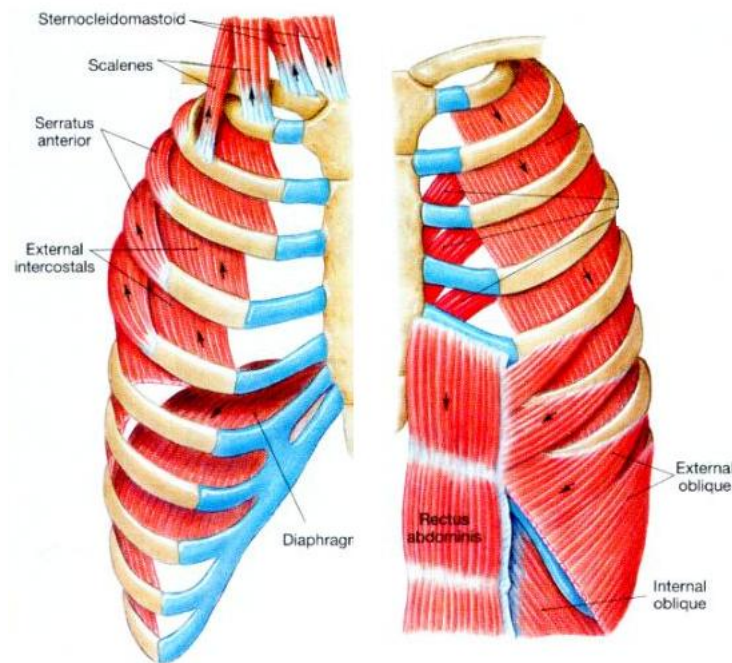


Figure 2.1: Breathing Muscles

2.4.2 Clinical Features of Respiratory Insufficiency

Symptoms of respiratory muscle weakness include breathlessness, hypoventilation, orthopnea, dyspnoea on minimal exertion and frequent nocturnal awakening. Clinical signs include tachypnoea, tachycardia, paradoxical breathing, accessory muscle use, reduced ribcage movement, perspiration and weight loss.

Hypoventilation is the inability of the body to maintain adequate alveolar ventilation to meet metabolic demands. It is characterised by an increase of arterial carbon dioxide in the blood. Hypoventilation occurs for three reasons. First, if respiratory muscle function is reduced; second, if there is an increase of the load on the respiratory muscles; and finally if there is a central drive impairment (Piper, 2010).

Hypoventilation first occurs during sleep when respiratory physiology is altered. The volume of air inspired per minute is reduced by approximately 10% in healthy subjects as the drive to breathe and respiratory centre responses to hypoxia and hypercapnia are reduced (Piper, 2010).

Respiratory muscle activation during non Rapid Eye Movement (REM) sleep and REM sleep is different to wakefulness breathing. The diaphragm is the primary muscle responsible for ventilation during this time. Nocturnal

physiological changes have little consequence to healthy subjects; however, they can cause significant ventilation changes to patients with respiratory muscle weakness such as patients with ALS (Schiffman and Belsh, 1993).

Oxygen desaturation, the first symptom of nocturnal hypoventilation, will become evident during REM sleep. Waking periods, poor sleep quality and reduced sleep duration occur. Changes in oxygen and carbon dioxide levels are limited initially by waking periods. Eventually, changes will occur during REM sleep because of a demand to sleep. Over time hypoventilation occurs during waking hours as the respiratory drive is depressed secondary to an increase in arterial carbon dioxide (Piper, 2010). Patients will complain of dyspnoea, orthopnoea, morning headache, daytime fatigue and excessive daytime sleepiness and will have physical signs such as tachypnoea, use of auxiliary respiratory muscles at rest and paradoxical respiration (Andersen et al., 2012). Changes in cognitive function have also been documented (Newsom-Davis et al., 2001).

Amyotrophic Lateral Sclerosis patients are initially asymptomatic despite respiratory muscle weakness (Schiffman and Belsh, 1993). Symptoms may not become apparent until later in the disease process. Respiratory muscle weakness was present in 86% of ALS participants at diagnosis but only 19.4% reported respiratory symptoms (Schiffman and Belsh, 1993). The respiratory system can adapt efficiently and, despite evidence of diaphragm dysfunction, Vital Capacity (VC) can be preserved (Similowski et al., 2000). Inspiratory neck muscle recruitment during wakefulness can compensate for diaphragm weakness and limit daytime symptoms (Similowski et al., 2000). Dyspnoea on exertion may be an initial symptom but this is less obvious as patients reduce their level of activity secondary to limb weakness. Dyspnoea at rest and reduced cough strength do not become obvious until later in the disease process (Hardiman, 2011).

2.4.3 Diagnosis of Respiratory Insufficiency

Respiratory assessments and monitoring is recommended for treatment and management of respiratory insufficiency. Tests to assess overall respiratory function, respiratory muscle strength and cough tests in ALS participants are available and are discussed in detail in Chapter 3.

2.4.4 Management of Respiratory Insufficiency

Symptoms of respiratory insufficiency should be assessed at each medical review (Andersen et al., 2012). Strategies to reduce symptoms can be recommended such as sleeping with additional pillows to reduce orthopnoea (Hardiman, 2011). Techniques to reduce the risk of aspiration include changing the consistency of food and liquids and advice regarding swallowing by the speech and language therapist. Excess and tenacious saliva can be managed with antimuscarinic medicine. Botulinum toxin A is recommended if antimuscarinic medicine is not effective. Excess secretions and saliva can be cleared from the upper airways with a suction machine (NICE, 2016). Further airway clearance management are discussed in 2.7.

Oxygen therapy is usually avoided in ALS patients as carbon dioxide retention can increase with oxygen therapy (Hough, 2013). Oxygen therapy should be provided only if the patient has symptomatic hypoxia (Andersen et al., 2012). The British Thoracic Society/Association for Chartered Physiotherapists in Respiratory Care (BTS/ACPRC) Guidelines recommend avoiding or exercising extreme caution when using oxygen therapy in NMD patients (Bott et al., 2009).

2.4.5 Non-Invasive Ventilation

Non-Invasive Ventilation (NIV) is the standard treatment for respiratory insufficiency in ALS. NIV is a form of bi-level positive airway pressure ventilator that provides intermittent positive pressure to support ventilation. NIV is recommended and prescribed to treat the signs and symptoms of respiratory muscle weakness by reducing work of breathing, improving gas exchange and improving sleep quality (NICE, 2016). The proposed criteria for NIV in ALS is detailed in Table 2.2.4.

Table 2.2.4 Proposed Criteria for Non-invasive Ventilation (Andersen et al., 2012)

<p>Symptoms/signs related to respiratory muscle weakness. At least one of the following</p> <p>Dyspnoea</p> <p>Tachypnoea</p> <p>Orthopnoea</p> <p>Disturbed sleep due to nocturnal desaturation/arousals</p> <p>Morning headache</p> <p>Use of auxiliary respiratory muscles at rest</p> <p>Paradoxical respiration</p> <p>Daytime fatigue</p> <p>Excessive daytime sleepiness >9</p>
<p>Abnormal respiratory function tests. At least one of the following</p> <p>Forced Vital Capacity <80% predicted value</p> <p>Sniff Nasal Inspiratory Pressure <40cmH₂O</p> <p>Maximal Static Inspiratory Pressure <60mmH₂O</p> <p>Significant nocturnal desaturation on overnight oximetry</p> <p>Morning blood gas pCO₂ >6kPa</p>

%=percent, cmH₂O= Centimetre of water, pCO₂=Partial Pressure of Carbon Dioxide, kPa=Kilopascal

NIV prolongs survival and improves QOL of ALS patients (Bourke et al., 2006). The effect of NIV on survival and QOL in 41 ALS patients was investigated by Bourke et al., (2006). Patients were randomised into a NIV group (n=22) or a standard care group (n=19) when they had symptoms of daytime hypercapnia and/or orthopnoea with a Maximal Static Inspiratory

Pressure (P_Imax) of less than 60%. There was a significant increase in survival and QOL in the NIV group. Mean survival was 48 days longer in the NIV group compared with the standard care group. Improvements in QOL measured with the short form 36 mental component summary and sleep apnoea QOL index symptoms exceeded the increase in survival. The greatest improvements in QOL were in the quality of sleep. NIV did not improve survival of patients with severe bulbar involvement. In this subgroup, QOL in the area of dyspnoea, daily functioning, social isolation and symptoms improved. Although, NIV did not improve survival in severe bulbar ALS patients, the authors concluded that NIV should be offered to these patients as there were improvements in aspects of QOL measures.

2.4.6 Invasive Mechanical Ventilation

Mechanical ventilation via a tracheostomy or an endotracheal tube prolongs survival. In an Italian cohort of ALS participants, the median survival was 16 months longer in tracheostomised than non-tracheostomised participants (Spataro et al., 2012). An improvement in QOL has not been established in tracheostomised patients and there is a danger that patients may develop a locked in syndrome (Kaub-Wittermer et al., 2003, Leigh et al., 2003). Locked in syndrome occurs when a patient is totally immobile including eye movements however, there are signs of undisturbed cortical function that can be measured by electroencephalogram (Bauer et al., 1979). The decision to proceed with invasive mechanical ventilation should be discussed early in the disease process before respiratory complications are present (Andersen et al., 2012). Ethical and clinical problems arise if respiratory failure occurs and end of life issues have not been discussed (Leigh et al., 2003). This discussion should take place with the patient, senior neurologist and a family member (Hardiman, 2011, Andersen et al., 2012).

High levels of financial and care resource are necessary. Emotional toll and increased caregiver burden is common (Kaub-Wittermer et al., 2003). The decision to proceed with invasive mechanical ventilation is individual. In Europe, 10% of ALS patients use mechanical ventilation (Chiò et al., 2010). It is not regularly prescribed in the United Kingdom (Leigh et al., 2003) or Ireland. Mechanical ventilation is commonly offered to patients in countries

where financial costs are provided by the State, such as Japan, where up to 33% of ALS patients use mechanical ventilation (Tagami et al., 2014).

2.5 Cough

2.5.1 Cough Mechanism

Cough is the rapid expulsion of air that removes irritants and secretions from the trachea, bronchi and lungs, and prevents aspiration of foreign substances. Cough can be voluntary and involuntary (Hough, 2013). It is defined by a motor act consisting of three phases; inspiratory, compressive and expulsive (Figure 2.2) (Morice et al., 2007).

The first phase, the inspiratory phase, is characterised by an inhalation of air. The volume of air inhaled can vary from 50% tidal volume to 50% VC. The diaphragm and intercostal muscles contract, the diaphragm domes and descends and decreases intrapleural and alveolar pressure. A pressure gradient is created between the alveoli and mouth and air is inhaled. The inhaled air lengthens the expiratory muscles (Hough, 2013, Ward et al., 2010).

Higher lung volumes will result in greater lengthening of expiratory muscles and generate higher intrathoracic pressures. However, large volumes of air are not always necessary and small volumes of inhaled air can generate sufficient intrathoracic pressures for an effective cough (McCool, 2006). There is a positive correlation between inspired and expired volumes of air (Hegland et al., 2013).

The compressive phase involves the closure of the glottis for 0.2 seconds. Intrathoracic pressure increases while maintaining lung volumes. Glottic closure minimises changes in muscle length by maintaining an isometric contraction of the expiratory muscles. The intrathoracic pressure generated during the compressive phase can be as high as 40kPa (McCool, 2006).

The expiratory phase commences with the reflexive opening of the glottis. The abdominal wall muscles (rectus abdominus, transverse abdominus, external oblique and internal oblique muscles) contract. The diaphragm muscle ascends passively, controlling the upward push of the abdominal

muscles. Air is released and the expiratory flow rate increases to reach peak expiratory flow (Hough, 2013).

The peak expiratory flow lasts 30 to 50ms and can reach flows of 720L/min (McCool, 2006). The peak expiratory flow and volume is determined by the inspired volume during the inspiration phase (Smith et al., 2012).

Subsequent expiratory flow is longer, lasting 200 to 500ms and at a reduced flow of 180 to 240L/min (McCool, 2006). This fast turbulent expiratory flow eliminates materials from the airways. The expiratory airflow must be sufficient to achieve effective airway clearance. The volume of air expired can be between 2 and 2.5 times greater than inspired volume. Air is expelled beyond the functional residual capacity, which is thought to increase the dynamic airflow at smaller proximal airways (Hegland et al., 2013).

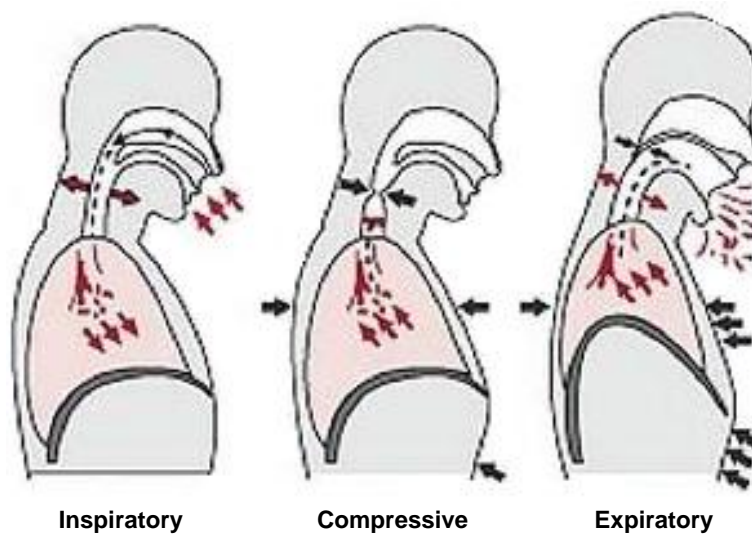


Figure 2.2: The Three Phases of a Cough

2.5.2 Normal Cough Reflex

The cough reflex is a complex mechanism comprising five components: cough receptors, afferent nerves, cough centre, efferent nerves and effector muscles (Hadjikoutis et al., 1999). Sensory nerve fibres located in the ciliated epithelium of the larynx, trachea pharynx and bronchial tree stimulate a cough. A cough pattern is determined by the location and the type of cough

stimulus. A cough stimulated in the upper airways results in an immediate expiration. An inspiratory phase is excluded to eliminate foreign material immediately to avoid aspiration. A stimulus below the larynx results in a large inhalation to create sufficient airflow to remove the stimulus (Polervino et al., 2012).

2.5.2.1 Cough in Amyotrophic Lateral Sclerosis

There are a number of factors that contribute to an ineffective cough in ALS patients. Firstly, inspiratory muscle weakness results in decreased inhalation volume. The inhalation phase of cough ideally requires volumes near to total lung capacity. A reduction in inhalation volume will reduce expiratory pressures and reduce expiratory air flow and velocity. The length tension ratio of the expiratory muscles and the optimum length to ensure recoil is not achieved. However, inspiratory muscle weakness is not as consequential as expiratory muscle weakness. Mild to moderate inspiratory weakness can have minimal impact on respiratory function measurements. Secondly, expiratory muscle weakness negatively impacts expiratory flow and pressures. The abdominal muscles do not shorten and contract but are relaxed and lengthened and therefore do not generate inter thoracic pressure. Thirdly, dynamic airway compression is reduced by expiratory muscle weakness (Hadjikoutis et al., 1999).

Cough is further complicated in bulbar ALS patients as a result of upper airway muscle weakness and co-ordination. Reduced laryngeal co-ordination prevents glottic closure and vocal cord adduction necessary for the compressive phase of cough. Reduced glottic closure results in an inability to maintain both isometric contraction of the expiratory muscles and intrathoracic pressure (Finder, 2010).

2.6 Respiratory Muscle Strength and Function, Cough Strength and Physical Function in Amyotrophic Lateral Sclerosis

In most ALS patients a combination of muscle weakness and an ineffective cough results in progressive respiratory and physical decline. Respiratory insufficiency and physical impairment in ALS can be assessed by a number of outcome measures. This is discussed in detail in Chapter 3. Common methods employed in the ALS population are VC to measure respiratory

function, Sniff Nasal Inspiratory Pressure (SNIP) to assess respiratory muscles strength, Peak Cough Flow (PCF) to quantify cough strength and ALSFRS-R to monitor physical function.

The rate of decline of VC percent predicted in ALS has been reported as 5.4% (Rafiq et al., 2015), 24% (Traynor et al., 2004) , 37.2% (Baumann et al., 2010), 42% (Schiffman and Belsh, 1993) and 49% predicted per year (Fitting et al., 1999). Despite a linear decline reported in VC percent predicted in three studies (Schiffman and Belsh, 1993, Traynor et al., 2004, Baumann et al., 2010) the VC percent predicted rates of decline differ greatly between the studies. The rate of SNIP decline has been reported as 50.4% per year of predicted values (Fitting et al., 1999). The rate of SNIP decline is linear (Bauer et al., 2012). There is limited published evidence on the rate of decline of PCF. In an RCT comparing M-IE and LVR, the rate of PCF decline has been reported as 69.24L/min per year in the LVR group with an improvement of 10.8L/min per year in the M-IE group (Rafiq et al., 2015). The results for the whole cohort were not provided. Physical function decline as measured by the ALSFRS-R ranges from a median 6.84 units per year in the first 17 months to 9.76 units per year in the first 18 months (Gordon et al., 2010). The rate of decline has been described as curvilinear with the most rapid decline was observed in the early and late phases of the disease (Gordon et al., 2010). More recently it has been described as linear with a steeper slope of decline identified in bulbar onset compared to spinal onset participants in an Irish ALS cohort (Rooney et al., 2016).

Research in ALS to date has described the rate of decline of VC, SNIP and ALSFRS-R. The rate of decline of VC and SNIP in an Irish ALS cohort has not been quantified and the rate of PCF decline has not been described in a large ALS cohort.

2.7 Airway Clearance Devices

An ineffective cough can impair the ability to effectively mobilise secretions; cause plugging of bronchi and increase the risk of respiratory infections. Chest infections further decrease cough strength and effectiveness in NMD participants (Bach and Saporito, 1996). An existing weak cough may not pose difficulties until a chest infection further decreases cough strength. M-IE

and LVR are recommended for airway clearance in patients with an ineffective cough such as NMD and ALS (Bott et al., 2009, Miller et al., 2009a, NICE, 2016, O'Callaghan et al., 2014).

The PCF value of 160L/min referred to in the BTS/ACPRC guidelines is known as the cough critical threshold. This is considered the minimum cough strength necessary to effectively clear secretions (Bott et al., 2009). A cough strength close to the cough critical threshold of 160L/min (Bach and Saporito, 1996) will be further reduced to below 160L/min to an ineffective cough in the event of a chest infection.

2.7.1 Mechanical Insufflation Exsufflation

Mechanical Insufflation Exsufflation (Figure 2.3) is a non-invasive cough augmentation device that applies positive and negative pressures to an individual's airway. A large inhalation is achieved with a positive pressure followed by a negative exhalation pressure (Figure 2.4) that creates a high expiratory flow rate and a high expiratory pressure gradient between the mouth and alveoli. It is thought that an increase in tidal volume reverses atelectasis, mobilises secretions and provides a stretch to the chest wall. The negative pressure or exsufflation phase aids expiratory flow. A high expiratory flow is created by a rapid shift from positive to negative pressure, simulating a natural cough to move secretions to the upper airways. The pressure is applied via a face mask, a tracheostomy or an endotracheal tube. If the expiratory flow achieved with M-IE is greater than that generated by an unassisted cough in neuromuscular disease patients, it can reduce the risk of pulmonary complications (Sancho et al., 2004). One cycle of M-IE typically consists of positive pressure followed by an exhale. This is repeated three to four times. A negative pressure is then applied and the patient is encouraged to actively cough during this phase. This cycle is repeated three to four times.



Figure 2.3: A M-IE Device

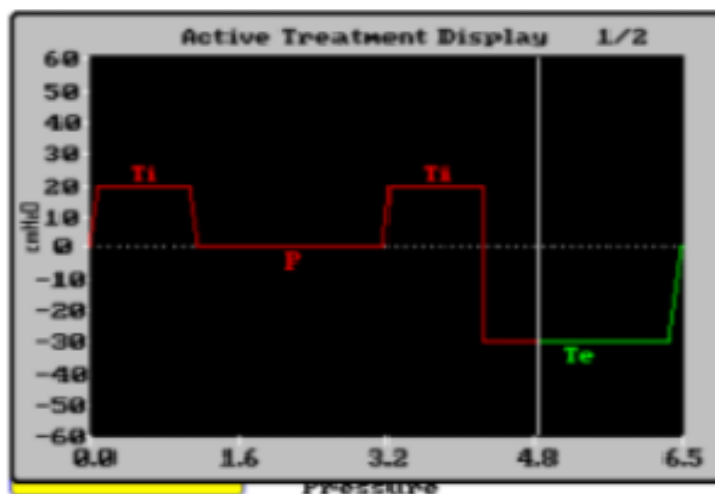


Figure 2.4: Screen of M-IE Depicting Two Positive Insufflations and a Negative Exsufflation

2.7.2 Lung Volume Recruitment

Lung Volume Recruitment (Figure 2.5) is a technique that maximises the volume of air inhaled and is thought to increase the strength of a cough by increasing the inhaled volume and providing the positive intrathoracic pressure required for an effective cough. LVR is performed with a resuscitator bag that is fitted with a one-way valve and a mask or

mouthpiece. In patients with poor bulbar function, who have an inability to close the glottis, maximum insufflation can be achieved only through one application or by using a one-way valve (Kang and Bach, 2000, Bott et al., 2009). The bag is compressed a number of times to stack breaths until a Maximum Insufflation Capacity (MIC) is achieved. Commonly 3–5 breaths are required to achieve MIC. A standard LVR treatment cycle includes 3–5 cycles of MIC followed by a cough. LVR is considered to improve the compliance and chest wall range of motion by increasing lung volumes. Increased lung volumes recruit collapsed lung segments, micro atelectasis is reversed and endomural flow improves (Kang and Bach, 2000).

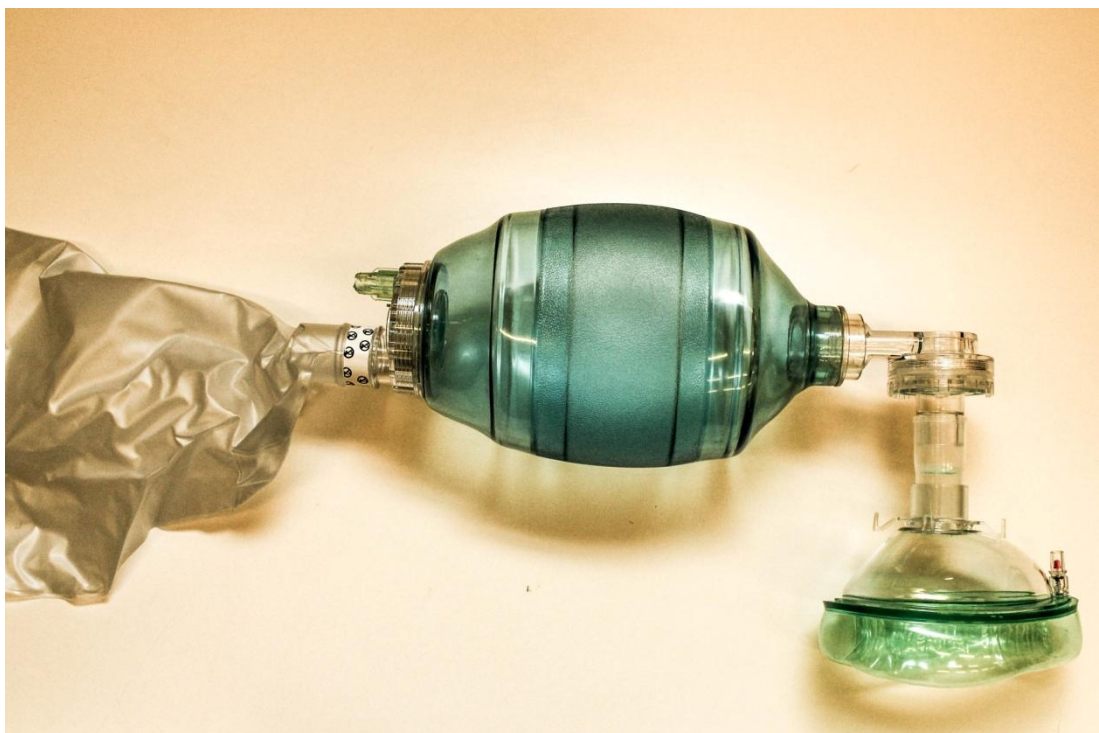


Figure 2.5: LVR Equipment

2.7.3 Mechanical Insufflation Exsufflation and Lung Volume Recruitment Prescription

The BTS/ACPRC guidelines advise that airway clearance strategies are introduced when PCF is equal to or less than 270L/min and that additional secretion management strategies are introduced when PCF is equal to or less than 160L/min in NMD participants (Bott et al., 2009). Airway clearance devices are recommended when PCF falls below 270L/min in ALS (Miller et al., 2009a). Irish Guidelines for the Physiotherapy Management of MND recommend the use of M-IE when secretions are causing uncomfortable

symptoms and there is an increase in the number of chest infections (O'Callaghan et al., 2014). The NICE MND Guidelines also describe introducing LVR when cough is ineffective and M-IE if LVR is not effective or during a chest infection (NICE, 2016).

Only one study has evaluated the frequency of M-IE prescription. Outpatient spinal cord injury participants were retrospectively evaluated. The frequency of M-IE prescription was 4.6% (41/883) (Crew et al., 2010) however, respiratory measures that could indicate M-IE prescription were not evaluated.

The BTS/ACPRC guidelines refer to the cough critical threshold of 160L/min (Bott et al., 2009). This PCF value was determined by the successful decannulation of 30 study participants: spinal cord injury (n=15), progressive NMD (n=11), guillain barre syndrome (n=2), obesity hypoventilation (n=1) and partial lung resection (n=1) (Bach and Saporito, 1996). Successful decannulation occurred only in participants with a PCF greater than 160L/min. Long term results described a high reliance on NIV and M-IE with 86% of the NMD participants requiring NIV for a mean of 16.8 hours per day and three NMD participants relied heavily on M-IE interventions.

The literature that explored M-IE in ALS did not use the cough critical threshold as this point for intervention. Criteria for M-IE included the use of NIV for two months (Senent et al., 2011) or evidence of respiratory failure as defined by criteria requiring NIV (Rafiq et al., 2015). Only one study specified a PCF measurement of less than 270L/min (Senent et al., 2011). The criteria for commencing LVR in ALS studies were participants who required NIV for a minimum of two months, had a PCF less than 270L/min (Senent et al., 2011) and had evidence of respiratory failure as defined by criteria requiring NIV (Rafiq et al., 2015).

When to commence airway clearance strategies is well documented (Bott et al., 2009, Miller et al., 2009a, O'Callaghan et al., 2014) but it is inconsistently applied in studies that explored the effect of M-IE and LVR in ALS. There is little evidence to support the clinical prescription practices implemented by clinicians in the ALS population. The frequency of M-IE and LVR prescription and associated respiratory muscle strength, function and morbidity, cough

strength, physical function or disease stage to prescribe M-IE and LVR in ALS participants in the clinical ALS setting has not been comprehensively explored or defined.

2.7.4 Evidence to support the use of Mechanical Insufflation

Exsufflation and Lung Volume Recruitment

A number of studies have investigated the use of M-IE and LVR in ALS and other NMD participants. Measurements that have been assessed include cough strength, VC, QOL, survival, number of chest infections, antibiotic use, hospitalisation rates, adherence and comfort. Participant clinical presentation has varied from those who are stable to critically ill ventilator-dependant, tracheostomy or NIV-dependant. The studies are discussed below.

Studies have demonstrated the role of M-IE in ventilator weaning and tracheostomy decannulation (Bach et al., 2015, Bach et al., 2014) in NMD participants. The prevention of tracheostomy insertion with a combination of M-IE or LVR in ALS (Bach, 1995) and Duchenne Muscular Dystrophy (Bach and Martinez, 2011) participants has also been demonstrated.

Bach et al., (2015) demonstrated that NMD participants who were considered unweanable from ventilator support could be successfully extubated with an intensive M-IE and NIV protocol. M-IE was administered every 60 minutes at pressures of 60–70cmH₂O until oxygen and carbon dioxide readings were normal. Participants were extubated and commenced on NIV support and continued with M-IE at pressures of 35–60cmH₂O every 30 minutes. Extubation was achieved in 97 of 98 participants in a mean of 3.4 days. This study established the usefulness of M-IE in NMD participants in the ICU setting although the regimen required considerable resources (Bach et al., 2015).

The combination of NIV and M-IE or LVR can avoid tracheostomies in ALS participants (Bach, 1995). ALS participants who avoided tracheostomies were compared with ALS participants who required tracheostomies. The participants who avoided a tracheostomy had 24-hour use of NIV and the use of cough augmentation devices such as M-IE and LVR with a Manually Assisted Cough (MAC). Participants who required a tracheostomy did not use NIV and cough augmentation devices or experienced acute respiratory

failure before NIV and cough augmentation devices were introduced. In addition, they had cough strength of less than 180L/min PCF and they could not achieve a MIC greater than VC. Similar findings were demonstrated in Duchenne Muscular Dystrophy participants with a combination of NIV and LVR (Bach and Martinez, 2011). These findings indicate that the respiratory impairments of ALS patients can be effectively managed using NIV and cough augmentation devices.

A number of studies have investigated the use of M-IE and LVR in stable non-ventilated ALS participants. One early study evaluated the use of M-IE in ALS participants in a prospective crossover study (Sancho et al., 2003). M-IE and tracheal suctioning was compared in six tracheostomy mechanically ventilated ALS participants. Suctioning followed by M-IE 30 minutes later was used for airway clearance to treat a chest infection. Oxygen saturations ($p<0.05$) and ventilator settings improved ($p<0.05$) and the volume of secretions removed was higher after M-IE than suctioning ($p=0.34$) when compared to baseline measurements. M-IE effect and comfort was subjectively rated higher by the participants than suctioning.

The findings of this study suggested that M-IE was safe to use in ALS patients with tracheostomies and that a combination of M-IE and suctioning improved oxygen saturations, ventilator settings and cleared secretions during a chest infection. There was a risk of bias as the treatments were not directly compared but assessed in combination. Suctioning was performed first followed by M-IE 30 minutes later. The oxygen saturations 30 minutes after suctioning and immediately prior to M-IE were not provided and therefore the improved results after M-IE cannot be attributed to M-IE alone. A Randomised Control Trial (RCT) with a larger sample size is required to accurately assess the effectiveness of suctioning versus M-IE in tracheostomy mechanically ventilated ALS patients.

Mechanical Insufflation Exsufflation was compared to assisted and unassisted coughing in 10 healthy and 47 ALS participants in a prospective randomised study (Mustfa et al., 2003). The interventions; maximal unaided cough, cough with a MAC, M-IE exsufflation only, M-IE insufflation only and

M-IE were performed randomly. Peak Cough Expiratory Flow (PCEF) was recorded.

Manually Assisted Cough, M-IE exsufflation only and M-IE significantly increased PCEF by 26% and 19% in bulbar ($p<0.05$) and by 28% and 21% in spinal participants ($p<0.001$). Baseline PCEF negatively correlated with M-IE exsufflation PCEF ($r=-0.593$, $p=0.001$) and M-IE PCEF ($r=-0.564$, $p=0.002$). Spinal participants with a VC of less than 50% and PCEF less than 160L/min had a greater percentage increase in PCEF with M-IE exsufflation and M-IE than bulbar participants.

This short-duration study revealed that M-IE increased cough strength more than an unassisted cough and there was a greater increase in weaker participants. However, lack of assessor blinding may have biased the results, there was no control group and M-IE settings were not published making direct comparison of studies difficult.

In a prospective cross over study of 26 ALS participants, PCF was measured after LVR without a one way valve and then after M-IE (Sancho et al., 2004). Both techniques were combined with a MAC. LVR increased PCF from 268.2 ± 138.6 L/min to 304.2 ± 138.6 L/min. M-IE decreased PCF from 268.2 ± 138.6 L/min to 225 ± 144.6 L/min. Stratification of the results identified that weaker participants improved their cough strength with M-IE. Participants with a PCF of less than 160L/min increased their PCF with M-IE and a MAC (130.8 L/min \pm 27 L/min to 153 ± 0.6 L/min). This study suggests that airway clearance devices may be more suitable to improve cough strength in weaker than stronger ALS participants.

In a prospective trial, Senent et al., (2011) assessed PCF, reported efficacy and comfort of seven cough techniques in 16 stable ALS participants. Unassisted cough, coached unassisted cough, coached cough combined with a MAC, LVR and a MAC, inspiratory volume by regular NIV settings and a MAC, NIV inspiratory positive pressure at 30 cmH₂O and combined with a MAC, and M-IE were performed.

Mechanical Insufflation Exsufflation generated the highest mean PCF (488L/min) followed by LVR combined with a MAC (284L/min). Both were

significantly higher than manual techniques ($p < 0.0001$). No significant differences were found between the bulbar and the spinal groups. Participants rated M-IE as the most effective treatment. All techniques were rated higher in the spinal group. Therapists did not correctly identify the most effective technique.

This study indicates that M-IE and LVR were well tolerated, they can immediately increase cough strength more than other techniques and they were equally effective for both bulbar and spinal participants. It highlights the importance of patient input when prescribing a cough augmentation technique as participants and not therapist identified the most effective technique correctly. This study had a small sample size and assessors were not blinded to interventions. Despite these criticisms this study portrayed a realistic clinical scenario.

In a one year RCT (Rafiq et al., 2015) forty participants were randomised into M-IE and LVR groups. The raw data suggested that there were favourable trends for both groups however definite conclusions cannot be made as the results were not significant. The LVR group had a lower number of chest infections ($p = 0.92$), and fewer number of days requiring antibiotics ($p = 0.926$), higher median survival ($p > 0.05$) and QOL ($p = 0.41$). In comparison, the M-IE group had a trend towards more favourable respiratory measurements. The average decline of Slow Vital Capacity (SVC) per month was lower in the M-IE group ($p = 0.47$) and there was an increase in PCF in the M-IE group but a decline in the LVR group ($p = 0.43$).

Statistically significant difference between M-IE and LVR were not found possibly for the following reasons. First, there was a small sample size and a high mortality rate of 69% in the M-IE group. Second, self-reported measures were used and all chest infections may not have been recorded (Yuen et al., 2013, Bollen et al., 2014). There was a high mortality rate and participants may have died of respiratory failure (Radunovic et al., 2013). Despite the non-statistically significant findings, this is the only RCT and long term study that evaluated clinically relevant measures of respiratory mortality and morbidity.

A repeated measure crossover study evaluated cough strength and pulmonary function among 29 ALS participants (Cleary et al., 2013). The intervention was LVR and the control intervention was a conversation with the assessor. FVC, SNIP and PCF were assessed immediately prior to intervention, and at 15 and 30 minutes following intervention. Significant increases in PCF were recorded at 15 and 30 minutes ($p=0.001$) and in FVC at 15 minutes ($p=0.0028$) following intervention. There was no change in SNIP ($p=0.264$).

This is a clinically significant study that has demonstrated that cough strength and pulmonary function can increase significantly for short durations of up to 30 minutes and 15 minutes respectively. It is however important to note the limitations of this study. Participants acted as their own control to assess treatment effect. There was a lower PCF treatment baseline at intervention; eleven participants had a baseline PCF of less than 180L/min compared to eight during the control assessments. Not all participants increased their PCF above the author's stated critical level of 180L/min (Cleary et al., 2013), indicating that LVR is not adequate to increase cough strength in all ALS participants.

Studies have investigated the effects of M-IE in ALS in combination with other conditions such as NMD (Sivasothy et al., 2001, Winck, 2004, Kaminska et al., 2015), Chronic Obstructive Pulmonary Disease (COPD) (Sivasothy et al., 2001, Winck, 2004) and healthy controls (Sivasothy et al., 2001). The studies are evaluated below.

Mechanical Insufflation Exsufflation, MAC and a combination of M-IE and MAC were compared in 29 healthy, COPD and NMD that included seven ALS participants. PCEF and reported effectiveness were assessed in this prospective randomised trial (Sivasothy et al., 2001).

Peak Cough Expiratory Flow of NMD participants without scoliosis increased with a MAC ($p<0.01$) and a combination of M-IE and MAC ($p<0.01$). There was a non-significant increase with M-IE alone ($p>0.05$). NMD participants without scoliosis reported that MAC and a combination of M-IE and MAC improved airway clearance.

ALS participants' results were not isolated but the NMD group without scoliosis was the most relevant. Reasons for a non-significant increase in cough strength with M-IE alone could be due to that PCEF was not assessed with the aid of the exsufflation phase and the M-IE settings were lower compared to other studies (Sancho et al., 2003, Sancho et al., 2004, Senent et al., 2011, Rafiq et al., 2015). This study established that MAC and a combination of M-IE and MAC can increase cough strength in NMD participants without scoliosis.

The effect of LVR on PCF, QOL and VC was assessed in 19 NMD participants including seven ALS, participants in a feasibility study (Kaminska et al., 2015). Participants had mild respiratory weakness and were instructed to perform LVR four times a day at home. There were non-significant increases in QOL ($p=0.09$), decreases in PCF ($p=0.18$) and decreases in FVC ($p=0.14$) in the ALS participants.

Limitations of this study include the small NMD participants sample size with an even smaller group of ALS participants ($n=7$) and adherence to a home exercise programme. Finally, the study duration of three months was too short to assess long term changes in respiratory function.

The physiological effects and tolerance of M-IE were assessed in 29 participants including 13 ALS, NMD and COPD participants (Winck, 2004). Cycles of M-IE at $\pm 15\text{cmH}_2\text{O}$, $\pm 30\text{cmH}_2\text{O}$ and $\pm 40\text{cmH}_2\text{O}$ pressure settings were applied consecutively in this prospective clinical trial. Outcome measures assessed included respiratory inductance plethysmography to measure respiratory breathing patterns, PCF, oxygen saturations, dyspnoea and VC.

In the ALS participants, PCF increased significantly with M-IE pressures at $\pm 40\text{cmH}_2\text{O}$ from a median of 170L/min to 200L/min ($p<0.005$). Oxygen saturations also increased ($p<0.005$) and breathing patterns did not deteriorate. PCF ($p<0.05$), oxygen saturations ($p<0.005$) and dyspnoea ($p<0.05$) improved significantly in NMD participants. In participants with COPD, PCF ($p>0.05$), oxygen saturations ($p<0.02$) and dyspnoea ($p<0.02$) improved with M-IE pressures at $\pm 40\text{cmH}_2\text{O}$.

This study established that M-IE is safe in COPD and NMD participants. It also demonstrated that M-IE at pressures of $\pm 40\text{cmH}_2\text{O}$ can increase PCF and oxygen saturations in ALS.

The literature examining M-IE and LVR in ALS indicates that both M-IE and LVR are safe and comfortable to use in mechanically ventilated, non-invasively ventilated as well as stable ALS patients (Sancho et al., 2003, Senent et al., 2011, Rafiq et al., 2015). MIE can increase cough strength more than an unassisted cough (Mustfa et al., 2003) and although an overall negative effect on PCF was identified in one study the technique was effective in weaker ALS participants (Sancho et al., 2004). LVR can also increase cough strength in addition to pulmonary function for short durations after treatment (Cleary et al., 2013). Analysis of the literature of M-IE and LVR and other conditions including ALS cannot form definite conclusions as the number of ALS participants within these studies was very small

It is unclear if one device is more superior to the other in ALS participants. Studies that compared M-IE and LVR had mixed results. LVR was more effective in increasing cough strength than M-IE in one study (Sancho et al., 2004) but less effective than M-IE in a second study (Senent et al., 2011). In the only RCT there was no statistically significant difference in cough strength, QOL, pulmonary function, survival, hospitalisation rates, number of chest infections and the number of days requiring antibiotics between the M-IE and LVR groups (Rafiq et al., 2015).

Manually Assisted Cough is commonly used with M-IE and LVR (Sancho et al., 2004, Senent et al., 2011). The comparison of M-IE and LVR combined with MAC techniques is difficult as MAC was used in one study (Sancho et al., 2004) but not in two (Mustfa et al., 2003, Rafiq et al., 2015). LVR but not M-IE was combined with a MAC in one study (Senent et al., 2011), which found a benefit of MAC in addition to LVR over LVR alone.

It is unclear whether these techniques are equally as effective in bulbar and spinal onset ALS. Results were stratified into bulbar and spinal groups in four studies (Mustfa et al., 2003, Sancho et al., 2004, Senent et al., 2011, Rafiq et al., 2015). M-IE and LVR were equally effective in increasing cough strength in both groups (Senent et al., 2011). M-IE had a greater effect on cough

strength in weaker spinal participants than stronger spinal and bulbar participants in a second study. The different components of M-IE revealed different findings for the groups and exsufflation only increased cough strength in bulbar participants (Mustfa et al., 2003). M-IE decreased and LVR increased cough strength for both bulbar and spinal in the study by Sancho et al., (2004). There was a non-statistically higher survival in bulbar LVR participants compared to bulbar M-IE participants; however this study was not powered for subgroup analysis (Rafiq et al., 2015). There is no trend among the studies to determine if bulbar or spinal participants are affected differently by M-IE and LVR.

Studies have primarily focused on the immediate outcomes of M-IE and LVR (Sancho et al., 2003, Mustfa et al., 2003, Senent et al., 2011, Cleary et al., 2013). Two studies have assessed outcome over a longer duration (Sancho et al., 2004, Rafiq et al., 2015). Rafiq et al., (2015) had a strong methodological construct but no significant difference between the interventions was identified. The study was small and had a high mortality rate which limited clear conclusions. Long term evaluation of respiratory outcomes and function remains limited.

2.8 Research Question

This literature review identified that M-IE is safe to use in mechanically ventilated ALS participants (Sancho et al., 2003) and M-IE and LVR are safe and comfortable to use in stable ALS participants (Sancho et al., 2003, Senent et al., 2011, Rafiq et al., 2015). Cough strength and pulmonary function can increase over short durations with M-IE and LVR (Mustfa et al., 2003, Cleary et al., 2013, Senent et al., 2011). However, it is unclear if one device is more superior to the other in ALS participants (Rafiq et al., 2015). There is no trend among the studies to determine if bulbar or spinal participants are affected differently by M-IE and LVR.

Given the areas explored to date, several gaps in the literature remain. The long term evaluation of respiratory muscle strength, function and morbidity and have not been described in an Irish ALS cohort. In addition, the long term evaluation of PCF in a large cohort has not been investigated. Studies have primarily focused on the immediate outcomes of M-IE and LVR

(Sancho et al., 2003, Mustafa et al., 2003, Senent et al., 2011, Cleary et al., 2013). Long term evaluation of respiratory outcomes and function remains limited. The rate of change of respiratory muscle strength, function, cough strength and physical function after the implementation of M-IE and LVR in ALS has not been assessed. Details on current practices of M-IE and LVR prescription in an Irish ALS population do not exist and the characteristics of ALS participants prescribed M-IE and LVR have not been examined. This research study planned to address the current gaps in the literature.

This study had two aims. The first aim was to measure respiratory muscle strength, function and morbidity, cough strength, physical function and outcome in an Irish ALS cohort. The second aim was to examine prescription practices in relation to M-IE and LVR devices and to compare the above characteristics in those prescribed such devices and those who were not.

The objectives were

1. To prospectively measure the changes in SNIP, SVC percent predicted, PCF, and ALSFRS-R over one year in a cohort of ALS patients
2. To measure the frequency of M-IE and LVR prescription
3. To identify the characteristics of participants at the time of M-IE and LVR prescription. This included time from diagnosis, site of onset, SNIP, SVC percent predicted, PCF and ALSFRS-R and respiratory symptoms
4. To compare the characteristics of the participants prescribed M-IE and LVR to participants not prescribed M-IE and LVR
5. To compare the rates of decline of SNIP, SVC percent predicted, PCF, and ALSFRS-R of participants prescribed M-IE and LVR to participants who were not prescribed M-IE and LVR.
6. To compare the number of chest infections reported and the number of antibiotics prescribed to treat them in all participants
7. To compare the number of chest infections and antibiotic used to treat them in participants prescribed M-IE and LVR to participants who were not prescribed M-IE and LVR
8. To determine the number of participants alive at study conclusion

The hypotheses were

1. There would be a statistically significant difference in disease characteristics of participants prescribed M-IE and LVR compared to participants not prescribed M-IE and LVR.
2. There would be a statistically significant difference in the rates of decline of SNIP, SVC percent predicted, PCF, and ALSFRS-R of participant's prescribed M-IE and LVR compared to participants not prescribed M-IE and LVR.
3. There would be a statistically significant difference in the number of chest infections and antibiotics used to treat them in participants prescribed M-IE and LVR to participants who were not prescribed M-IE and LVR.

2.9 Conclusion

This chapter has provided a narrative review of the ALS population and the associated respiratory complications; it has critically appraised the literature relevant to M-IE and LVR and highlighted the existing gaps in the literature. Finally, the hypotheses and objectives have been outlined. Chapter 3, the development of the methodology, will describe the outcome measures available for assessment and justify their use in this research study.

Chapter 3: Respiratory Measurements, Physical Function and Airway Clearance Device Prescription over One Year in Amyotrophic Lateral Sclerosis: Development of Methodology

3.1 Introduction

This chapter outlines the development of the methodology and describes and critically evaluates relevant outcome measures available for assessment in the Amyotrophic Lateral Sclerosis (ALS) population. The chosen outcome measures are detailed and their use in this research study is justified. The aims of this study required that high quality sensitive data on respiratory measures be collected, with a maximum quantity of data to be gathered while minimising burden on the participants recruited.

3.2 Tests of Overall Respiratory Function

The American Thoracic Society and European Respiratory Society (ATS/ERS) published a joint statement on respiratory muscle testing in 2002. Dynamic spirometry and maximum flow, maximum voluntary ventilation, carbon monoxide transfer, exercise testing and static lung volumes assess overall respiratory function (ATS/ERS, 2002). Table 3.1 summarises the assessments available and details their advantages and disadvantages. Slow Vital Capacity (SVC), a static lung volume was chosen to assess overall respiratory function in this research study.

Table 3.1: Tests of Overall Respiratory Function, their Purposes, Advantages and Disadvantages

Overall respiratory function tests	Equipment	Purpose	Advantages	Disadvantages
Dynamic spirometry and maximum flow	Spirometer	Diagnoses restrictive and obstructive pulmonary disease	Differentiates between different respiratory conditions	Spirometry loop does not provide a quantitative measurement Interpretation is variable
Maximum voluntary ventilation	Spirometer	Measures total volume of air exhaled during 12 seconds of rapid, deep breathing	Differentiates between different respiratory conditions	Effort dependant Tiring Not recommended for assessment of overall respiratory function (ATS/ERS, 2002)
Arterial blood gases	Phlebotomy skills and laboratory analysis	Measure the oxygen, carbon dioxide and acidity levels in blood (Hough, 2013)	Sensitive to severe respiratory weakness Normal values available	Low sensitivity to mild to moderate respiratory weakness (ATS/ERS, 2002)
Overnight pulse oximetry	Portable pulse oximeter	Screens oxygen levels at night	Inexpensive	
Polysomnography	Polysomnography	Records brain, heart and limb activity		Expensive
Carbon monoxide transfer	Spirometer Pneumotachometer	Measures the lungs ability to transfer gas to cells in the pulmonary capillaries	Provides absolute levels of ventilation and perfusion (Macintyre et al., 2005)	Low specificity (ATS/ERS, 2002)
Exercise testing	Specialised equipment; cycle ergometer and cardio and respiratory stress test	Confirms and quantifies exercise incapacity	Assessment of dynamic, moderate to high intensity exercise for a prolonged period of time	Poorly standardised in NMD participants (ATS/ERS, 2002)
Static lung volumes	Spirometer	Measures lung volumes	Monitors respiratory muscle weakness (ATS/ERS, 2002) Standardised technique (Miller et al., 2005) Normal values Prognostic indicator (Capozzo et al., 2015) Predicts survival (Baumann et al., 2010)	Limited in bulbar participants (Morgan et al., 2005) Insensitive to mild to moderate respiratory weakness (Fitting et al., 1999)

NMD=Neuromuscular Disease, ATS/ERS=American Thoracic Society/European Respiratory Society

3.2.1 Vital Capacity

Vital Capacity (VC), a static lung volume that is defined as the volume of air exhaled after a maximal inspiration (Hough, 2013). Inspiratory muscle weakness decreases the inhalation volume and expiratory muscle weakness inhibits full expiration (ATS/ERS, 2002) and as a result, VC is the most frequently abnormal static lung volume (ATS/ERS, 2002). Other static lung volumes measurements are; total lung capacity, residual volume and functional residual capacity. Functions of VC include assessment of overall respiratory function (ATS/ERS, 2002), diagnosis of respiratory dysfunction and monitoring of respiratory muscle weakness (Miller et al., 2005). Regular VC assessment is recommended in the ALS population (Andersen et al., 2012, NICE, 2016).

There are two methods to measure VC, Forced Vital Capacity (FVC) and SVC. FVC measures the volume of air forcibly exhaled after a maximal inspiration (Hough, 2013) and is the most frequently used respiratory measurement in ALS (Miller et al., 2009b, Andersen et al., 2012).

Alternatively, SVC is the maximum volume of air that can be inspired or expired from a relaxed manoeuvre. SVC assessments have also been used in ALS studies (Rafiq et al., 2015) and as a secondary outcome measure in clinical trials of ALS (Lauria et al., 2015, Dupuis et al., 2012). In contrast to the slow manoeuvre, FVC can be difficult and fatiguing for patients with a Neuromuscular Disease (NMD). The difference between FVC and SVC is minimal and both assessments can be used for the evaluation of ALS participants (NICE, 2016). In a study of healthy subjects, there was a non-significant difference in the volume of FVC and SVC. It was identified that SVC was on average 1.9% higher than FVC (Chhabra, 1998).

Vital Capacity is commonly used for regular monitoring of respiratory status in ALS (Miller et al., 2009b). It can predict survival (Baumann et al., 2010) and can be a prognostic indicator of death or requiring a tracheostomy within one year in ALS (Morgan et al., 2005, Traynor et al., 2004, Capozzo et al., 2015). An initial rate of VC percent predicted decline of greater than 2% per month in the first three months of a study was associated with a higher mortality rate of 47% compared to a mortality rate of 8% in participants with

an initial decline of less than 2% per month. A 1% increase in yearly rate of VC percent predicted decline was associated with a risk of mortality of 17.3% (Traynor et al., 2004). Death or requiring a tracheostomy was more likely in participants with a VC of less than 75.9% predicted value at baseline (Capozzo et al., 2015). A VC of less than 50% predicted was a predictor of death after six months with 58% sensitivity and 96% specificity (Morgan et al., 2005).

Additionally, reference equations to calculate normal predictive values for VC are available and have been published in a number of populations (Pellegrino et al., 2005). Although the ATS/ERS committee do not recommend any specific European reference equations (Pellegrino et al., 2005), the European Community for Coal and Steel (ECCS) reference values and the combined reference equations from the 1993 (ERS) publication were chosen for this research study as they are commonly used for reference equations for the European population (Quanger et al., 1993) Table 3.2.

Table 3.2: Summary equations for vital capacity for adults aged 18-70 years (Quanger et al., 1993)

	Regression Equation	RSD	1.64RSD
Men	$5.76H - 0.026A - 4.34$	0.61	1.00
Women	$4.43H - 0.026A - 2.89$	0.43	0.71

H=Height, A=Age in years, RSD=Residual Standard Deviation. The lower five and upper 95 percentile are obtained by subtracting or adding the figure in the last column from the predicted mean

A further practical advantage of VC measurement is the standardised VC assessment (Miller et al., 2005) and the available training. The ATS/ERS 2005 guidelines have in depth test procedures to ensure high inter and intra-rater reliability standards (Miller et al., 2005). To ensure this high standard, The Irish Association of Respiratory Scientists (IARS) in Ireland recommend that assessing healthcare clinicians should undertake a six month spirometry training programme to ensure high standards of spirometry performance

(IARS, 2016). This six month spirometry training programme was completed by the lead researcher to comply with these standards.

A clinically significant advantage of VC measurement is its contribution to the assessment of Non-Invasive Ventilation (NIV) initiation in ALS (NICE, 2016, Andersen et al., 2012). The criteria for initiating NIV in ALS requires the presence of respiratory muscle weakness symptoms, and at least one of the following respiratory function tests; a VC of less than 80% predicted, a Sniff Nasal Inspiratory Pressure (SNIP) less than 40cmH₂O, PIMax less than 60mmH₂O, significant nocturnal desaturation on overnight oximetry or morning blood gas partial pressure of carbon dioxide greater than 6 kilopascals of mercury (Andersen et al., 2012).

Having considered the favourable aspects of VC it is important to note its limitations. Firstly, it is not sensitive in detecting all levels of respiratory muscle weakness. Mild to moderate respiratory weakness can go undetected as it does not reduce total lung capacity to a significant detectable level. A participant can have normal predicted values with mild to moderate respiratory involvement (Fitting et al., 1999, Polkey et al., 1998). Secondly, in bulbar dysfunction, VC cannot be performed by all participants (Morgan et al., 2005) as a result of difficulties creating a tight lip seal around the mouth piece. VC could not be performed by 14% ALS participants in the evaluation in this study; authors concluded that this was as a result of bulbar weakness. However, a facemask can be used to avoid this problem (Lyall et al., 2001).

To summarise, VC measures overall respiratory function but has both advantages and disadvantages. VC is the most widely used test in ALS research (Andersen et al., 2012, Miller et al., 2009b) because it is commonly available and easy to perform in the majority of ALS participants. It is a prognostic indicator and it can predict survival in ALS (Morgan et al., 2005, Traynor et al., 2004, Capozzo et al., 2015). Recognised reference values are published (Quanger et al., 1993) and it has excellent standardisation to ensure high inter and intra-rater reliability (Miller et al., 2005). It is also used to determine the need for NIV in ALS (Andersen et al., 2012, NICE, 2016). However, it is not sensitive in detecting mild respiratory changes (Fitting et al., 1999, Polkey et al., 1998) and it can be difficult to perform in participants

with bulbar dysfunction (Morgan et al., 2005). The forced method can also be fatiguing and tiring. Therefore, SVC with the use of a facemask was chosen as the method of choice to assess overall respiratory function.

3.3 Tests of Respiratory Muscle Strength

Monitoring of respiratory muscle weakness is recommended in conditions such as ALS to guide therapeutic interventions (Bott et al., 2009, ATS/ERS, 2002, Miller et al., 2009b) and muscle strength can be assessed by non-volitional and volitional tests. Non-volitional tests include phrenic nerve stimulation and abdominal muscle activation. Volitional tests include Maximal Static Inspiratory Pressure (PImax) and Maximal Static Expiratory Pressure (PEmax) and SNIP.

3.3.1 Non-Volitional Tests of Respiratory Muscle Strength

3.3.1.1 Phrenic Nerve Stimulation

Phrenic nerve stimulation isolates activation of the diaphragm. It can be stimulated transcutaneously, magnetically or by twitch transdiaphragmatic pressure. This non volitional test has the advantage of being participant effort independent. However, it is widely unavailable as it is expensive and can be invasive, uncomfortable and time consuming to perform (ATS/ERS, 2002).

3.3.1.2 Abdominal Muscle Stimulation

Electrical stimulation directly to the abdominal muscle gives a non-volitional assessment of abdominal muscle strength. It is difficult to activate all abdominal muscles and it can be a painful assessment. Alternative non-volitional abdominal muscle activation is the magnetic activation of the eighth to tenth thoracic vertebrae and measuring the corresponding twitch gastric pressure.

3.3.2 Volitional Tests of Respiratory Muscle Strength

3.3.2.1 Maximal Static Inspiratory and Expiratory Pressure

Maximal Static Inspiratory Pressure and PEmax measure the maximum inspiratory and expiratory pressure sustained for 1.5 seconds (Hough, 2013). A PImax manoeuvre is achieved through a mouth piece from residual volume

in a seated position. The maximum value of three manoeuvres within 20% of each other is recorded. PEmax is measured during a similar manoeuvre from total lung capacity.

A number of advantages exist with PImax and PEmax pressure tests. They are easy and simple to perform, normal values based on age and gender are available (Black and Hyatt, 1969), they are widely used in research (Senent et al., 2011, Sancho et al., 2004) and they correspond to transdiaphragmatic pressure (ATS/ERS, 2002). However, maintaining an adequate seal around the mouthpiece, particularly in bulbar ALS participants is difficult, limiting its application. PImax is a global inspiratory muscle assessment and it cannot specifically identify the inspiratory muscles recruited. Maximal volitional effort is required and results can lack specificity if the participant's effort is sub-maximal (ATS/ERS, 2002). In the present study, assessments that did not use a mouthpiece were required thus PImax and PEmax were excluded to assess respiratory muscle strength.

3.3.2.2 Sniff Nasal Inspiratory pressure

Sniff Nasal Inspiratory Pressure measures peak inspiratory nasal pressure. This pressure reflects the pressure in the nasopharynx, an indicator of alveolar pressure, thus assessing respiratory muscle strength (ATS/ERS, 2002). It is used widely in ALS research (Bourke et al., 2006, Georges et al., 2016, Senent et al., 2011, Cleary et al., 2013) and it is considered an easy to perform assessment and one that can be performed by all patients (ATS/ERS, 2002) including those with a NMD (Stefanutti et al. 2000).

Normal SNIP values in healthy adults have been calculated and can be predicted from age and sex, they negatively correlate with age and are independent of body mass index and height (Uldry and Fitting, 1995). Healthy Caucasian children values are similar to adults (Stefanutti and Fitting, 1999).

Other respiratory muscle strength tests and overall respiratory function assessments correlate with SNIP. SNIP has been shown to correlate with transdiaphragmatic pressure ($r^2=0.65$) (Morgan et al., 2005), overnight pulse oximetry ($r=0.4$) and FVC ($r=0.47$) (Capozzo et al., 2015), VC decline

($r=0.85$) (Chaudri et al., 2000), arterial carbon dioxide tension ($r=-0.6$) in ALS participants and P_Imax ($r=0.94$) in NMD participants (Hart et al., 2003).

Practical clinical applications of SNIP measurements are commonly utilised. A SNIP less than 40cmH₂O in combination with subjective respiratory symptoms related to muscle weakness is used to determine the need for NIV in ALS patients (Andersen et al., 2012, Miller et al., 2009b). SNIP can be used to monitor respiratory decline in bulbar patients (Andersen et al., 2012), it can detect early respiratory involvement (Fitting et al., 1999) however this is less sensitive in severe bulbar dysfunction participants (Lyll et al., 2001). SNIP is a prognostic indicator in ALS (Morgan et al., 2005, Capozzo et al., 2015), death or requiring a tracheostomy within one year was associated with a baseline SNIP score of 34cmH₂O (Capozzo et al. 2015). Death within six months was associated with a SNIP less than 40cmH₂O and a median survival of three months was associated with a SNIP less than 30cmH₂O (Morgan et al., 2005).

Oesophageal Pressure during Maximal Sniffs (Pes) has been validated against SNIP (Heritier et al., 1994). There was a strong positive linear relationship ($r= 0.96$) between Pes and SNIP in healthy, NMD and skeletal disorder participants. SNIP had a good within and between session reproducibility after one month as assessed in 10 healthy participants (Maillard et al., 1998).

Sniff Nasal Inspiratory Pressure is reproducible. SNIP values were reproducible one day and one month after initial assessment in 10 healthy participants (Maillard et al., 1998). In advanced stages of ALS 95.7% of participants could perform reproducible SNIP tests in comparison to only 75.9% and 83.3% of participants performing reproducible FVC and P_Imax respectively (Morgan et al., 2005). ALS patients can perform SNIP in advanced disease stages (Capozzo et al., 2015). In advanced ALS disease FVC was assessed in 86%, P_Imax in 81% of and SNIP in 96% of participants, suggesting SNIP is easier to perform in advanced ALS disease (Morgan et al., 2005).

Reliability and acceptability were assessed in older healthy adults. Intra-rater (Intraclass Correlation Coefficient (ICC) = 0.76) and inter-rater reliability (ICC

= 0.88) of SNIP was good. Reliability co-efficients were based on five assessments compared to the recommended 10 assessments to overcome a learning effect (Lofaso et al., 2006). There is a learning effect associated with SNIP as assessed in a feasibility study of SNIP for ALS clinical trials. SNIP values were below normal at baseline but remained at baseline or above normal after three months in contrast to the ALSFRS-R and FVC that declined in parallel (Bauer et al., 2012). In healthy participants, a learning effect was also established after seven assessments, concluding that 10 assessments should be performed in healthy subjects (Uldry and Fitting, 1995). In contrast, a second study established a learning effect after 10 assessments in 325 healthy and NMD and lung disease participants. Recommendations from this study were to perform 10 additional assessments if the value was below normal in the first 10 assessments or if it is being used to assess respiratory decline over time (Lofaso et al., 2006).

The assessment of SNIP can be performed with an occluded or an open nostril. It is recommended to assess SNIP with an open nostril by the European Network for the Cure of ALS (ENCALS) (Appendix 1) and the ATS/ERS (ATS/ERS, 2002). Variability of SNIP techniques can affect interpretation of different studies. In one study a commercial SNIP meter was also not available and the opposite nostril was occluded (Morgan et al., 2005), this is in comparison to other studies where the opposite nostril was open (Hart et al., 2003, Barnes et al., 2014, Stefanutti et al., 2000, Maillard et al., 1998). It is also recommended to perform SNIP in a sitting position by the ENCALs and ATS/ERS (ATS/ERS, 2002) although SNIP values were similar in sitting and lying in healthy adults (Uldry and Fitting, 1995). Studies related to Mechanical Insufflation Exsufflation (M-IE) and Lung Volume Recruitment (LVR) have assessed SNIP in sitting (Senent et al., 2011, Sancho et al., 2004).

Participant physical difficulties can limit SNIP assessments. Difficulties include an inability to close the mouth sufficiently or upper airway collapse, dyspraxia, deviated nasal septum, nasal obstruction and a large nostril that cannot hold a nasal probe (Chaudri et al., 2000, Morgan et al., 2005, Fitting et al., 1999). In one series, eight (3.1%) NMD participants were unable to perform SNIP (Hart et al., 2003). Although, a lip seal is not required, bulbar

patients can also find it difficult to perform the appropriate technique. SNIP results were lower in bulbar participants ($30 \pm 14.3\%$ predicted) compared with the non-bulbar participants ($46.2 \pm 24.1\%$ predicted). Bulbar and non-bulbar groups had an equal number of hypercapnic participants but SNIP scores were lower in the bulbar group suggesting that it was not as a result of respiratory weakness but as a result of poor SNIP technique (Chaudri et al., 2000). Other studies have reported ease of NMD and skeletal disorder participants when performing SNIP (Stefanutti et al., 2000).

There are limitations associated with SNIP it has a low sensitivity in severe bulbar dysfunction participants (Lyll et al., 2001), it has a learning effect (Lofaso et al., 2006) and it is effort dependant. Despite these limitations, SNIP using the open nostril technique in a seated position was chosen as the assessment tool for respiratory muscle strength for the following reasons. It has been shown that SNIP is more sensitive than VC in detecting early respiratory involvement (Chaudri et al., 2000); it is easy to perform (Stefanutti et al., 2000); it is tolerated in advanced stages of ALS (Fitting et al., 1999, Capozzo et al., 2015); it is widely used in ALS research and it has been approved for use in research (ATS/ERS, 2002).

In conclusion, in the ALS population, it is not suitable to use SNIP in isolation to assess respiratory muscle strength; complimentary respiratory muscle strength assessments should be measured in tandem (Chaudri et al., 2000). Consequently, for the purpose of this research, SNIP and VC were employed in combination for a more comprehensive assessment of respiratory muscle strength and overall respiratory function.

3.4 Cough Tests

Peak expiratory flow, cough pressures and Peak Cough Flow (PCF) assess cough strength. The advantages and disadvantages of three assessments are discussed below.

3.4.1 Peak Expiratory Flow

Peak expiratory flow is the maximum flow achieved from a forced expiration from a maximum inspiration with an open glottis. It can be an indication of airway obstruction (Hough, 2013). Maximum expiratory flow volume curve

obtained during FVC can be used to determine the peak expiratory flow. A peak flow meter can also be used.

3.4.2 Cough Pressures

Cough pressures can be measured at the oesophagus or stomach. Cough pressures are invasive assessments that involve inserting a balloon catheter into the oesophagus or stomach with a local anaesthetic (Man et al., 2003). Cough pressures were not utilised in this study as a result of the invasive nature.

3.4.3 Peak Cough Flow

Peak Cough Flow is the peak flow generated with a cough through a peak flow meter (Bott et al., 2009) in contrast to a peak expiratory flow which is the flow generated from a forced expiration.

Cough effectiveness can be assessed by PCF (Andersen et al., 2012). Regular PCF assessment is recommended in ALS (O'Callaghan et al., 2014, NICE, 2016) and in NMD patients (Bott et al., 2009) and it has been used widely in studies evaluating cough augmentation techniques in ALS (Senent et al., 2011, Cleary et al., 2013, Rafiq et al., 2015, Sancho et al., 2003).

Cough stomach pressure, spirometry, PImax and PEmax correlates with PCF among NMD and ALS participants. PCF correlated with FVC ($r=0.72$) and forced expiratory volume in one second ($r=0.69$) in children with Duchenne Muscular Dystrophy (Gauld and Boynton, 2005). PCF correlated with PEmax ($r=0.77$), cough stomach pressure ($r=0.7$) and PImax ($r=0.74$) in NMD participants (Tzani et al., 2014). In ALS PCF correlated with PEmax ($r=0.53$) and PImax (Park et al., 2010).

Reduced cough strength can be detected and an ineffective cough can be predicted by a PCF assessment in ALS (Sancho et al., 2007). It also considered a sensitive assessment tool. PCF, PImax, PEmax cough stomach pressure were assessed in 49 NMD, including 9 ALS participants. PCF detected a higher number of weak PCF values compared to PEmax and cough stomach pressure, indicating that PCF was more sensitive than PEmax and cough stomach pressure in detecting weak cough (Tzani et al.,

2014). A PCF of 255L/min in stable ALS participants can predict the risk of an ineffective cough during a respiratory tract infection. VC, PImax and MEP did not predict the risk of ineffective cough (Sancho et al., 2007).

Recently PCF has shown some potential to predict survival in ALS. A pilot study investigating the effects of M-IE and LVR in ALS participants found that a PCF greater than 160L/min had a better median survival of 260 days versus 110 days ($p=0.000$) in participants with PCF less than 160L/min (Rafiq et al., 2015).

PCF was chosen as the outcome measure for cough strength for multiple reasons. It is clinically relevant, regular PCF assessment is recommended in ALS (O'Callaghan et al., 2014, NICE, 2016). Also, it has been widely used in ALS research (Senent et al., 2011, Cleary et al., 2013, Rafiq et al., 2015, Sancho et al., 2003), it correlates with other respiratory muscle tests (Park et al., 2010); it is sensitive in detecting cough strength changes and predicting an ineffective cough in ALS participants (Sancho et al., 2007). Finally, it may predict survival in ALS patients (Rafiq et al., 2015).

3.5 Physical Function

3.5.1 Amyotrophic Lateral Sclerosis Functional Rating Scale Revised

The ALSFRS-R is a 12 item scale that assesses participants self-reported levels of function in their home (Appendix 2). The ALSFRS-R has been used as both a primary (Traynor et al., 2004) and secondary (Shefner et al., 2004) outcome measure in clinical trials.

The ALSFRS-R consists of 12 questions (yielding a maximum score of 48) that measure aspects of the participants' life. Each question is given a score of zero to four, four being normal function. The original 10 item scale, ALSFRS, was originally designed to assess areas of feeding, self care, ambulation and communication (Cedarbaum and Stambler, 1997). The ALSFRS was revised to incorporate respiratory involvement as it was disproportionally weighted to limb and bulbar symptoms questions. Additional respiratory questions were added to the ALSFRS to evaluate dyspnoea, orthopnoea and the need for ventilator support (Cedarbaum et al., 1999).

The ALSFRS-R decreases rapidly in ALS and can predict survival (Kaufmann et al., 2005, Gordon et al., 2004, Cedarbaum et al., 1999, Traynor et al., 2004). Participants who had a baseline ALSFRS-R score of less than a median of 38 were 4.4 times more likely to die or require a tracheostomy within the one year study ($p < 0.001$) (Kaufmann et al., 2005). Participants with a score above 38 at baseline had a mean survival of 25.2 months compared to a mean survival of 14.6 months with a score below 38.

The reliability of ALSFRS-R is excellent. Nine ALS participants were assessed with the ALSFRS-R by 19 primary assessors and 11 back up assessors. The results revealed excellent inter-rater (ICC=0.93; 95% CI 0.84–0.98), intra-rater (ICC=0.95; 95% CI 0.92–0.98) and telephone administration reliability (ICC=0.97; 95% CI 0.93–0.98) as a primary outcome measure in ALS clinical trials (Kaufmann et al., 2007).

The ALSFRS-R is internally consistent and has strong construct validity (Cedarbaum et al., 1999). Cedarbaum et al. 1999 evaluated 387 placebo controlled participants in a clinical trial. Monthly assessments included ALSFRS, ALSFRS-R and the Sickness Impact Profile. The ALSFRS-R demonstrated internal consistency (Cronbach's $\alpha = 0.73$) and negatively correlated with Quality of Life (QOL) measured by the Sickness Impact Profile ($r = -0.72$), indicating a strong construct validity.

Due to its common use in research (Shefner et al., 2004), its ability to predict survival (Kaufmann et al., 2005), its excellent inter-rater and intra-rater reliability (Kaufmann et al., 2007), internal consistency and construct validity (Cedarbaum et al., 1999), ALSFRS-R was employed to assess function in this research study.

3.6 Outcome

The literature review in Chapter 2 has highlighted the limited evaluation of clinically relevant measures of respiratory morbidity and mortality with M-IE and LVR use in ALS. Only one study has evaluated chest infection frequency, the number of days requiring antibiotics, hospitalisations and survival (Rafiq et al., 2015). The frequency of chest infections and antibiotics was explored in this research study to add to this limited knowledge of

respiratory morbidity with M-IE and LVR use in ALS. Both self-report measures and information from the participants' General Practitioner (GP) were employed. Two methods were selected to limit the errors in collecting data associated with both methods. Self-report methods can be inaccurate (Yuen et al., 2013, Bollen et al., 2014). All chest infections may not have warranted a visit to a GP and all chest infections records may not have been gathered by a GP. Outcome was thus determined by 1) the number of chest infections and antibiotics used during the study period, 2) the number of participants alive at study conclusion.

3.7 Conclusion

This chapter of the thesis has justified the study design and reviewed and critically evaluated the available outcome measures for the assessment of overall respiratory function, respiratory muscle weakness, cough strength, function and outcome in ALS. SVC, SNIP, PCF, ALSFRS-R, chest infection frequency, antibiotic use and the number of participants alive at study conclusion were selected as the most suitable outcomes for this research study. In Chapter 4, the methodology of each of these assessments will be detailed.

Chapter 4: Respiratory Measurements, Physical Function and Airway Clearance Device Prescription over One Year in Amyotrophic Lateral Sclerosis: Methodology

4.1 Introduction

This chapter will outline the design of the study, the selection of participants, the assessment procedure, data collection and analysis.

4.2 Study Design

A prospective longitudinal and observational cohort study addressed two study aims. The first aim of the study was to measure respiratory muscle strength, function and morbidity, cough strength, physical function and outcome in an Irish Amyotrophic Lateral Sclerosis (ALS) cohort over one year. The second aim was to examine prescription practices in relation to Mechanical Insufflation Exsufflation (M-IE) and Lung Volume Recruitment (LVR) devices and to compare the above characteristics in those prescribed such devices and those who were not.

4.3 Objectives and Hypotheses

The objectives were:

1. To prospectively measure the changes in Sniff Nasal Inspiratory Pressure (SNIP), Slow Vital Capacity (SVC) percent predicted, Peak Cough Flow (PCF), and Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R) over one year in a cohort of ALS patients
2. To measure the frequency of M-IE and LVR prescription
3. To identify the characteristics of participants at the time of M-IE and LVR prescription. This included time from diagnosis, site of onset, SNIP, SVC percent predicted, PCF and ALSFRS-R and respiratory symptoms
4. To compare the characteristics of the participants prescribed M-IE and LVR to participants not prescribed M-IE and LVR
5. To compare the rates of decline of SNIP, SVC percent predicted, PCF, and ALSFRS-R of participants prescribed M-IE and LVR to participants who were not prescribed M-IE and LVR.

6. To compare the number of chest infections reported and the number of antibiotics prescribed to treat them in all participants
7. To compare the number of chest infections and antibiotics used to treat them in participants prescribed M-IE and LVR to participants who were not prescribed M-IE and LVR
8. To determine the number of participants alive at study conclusion

The hypotheses were:

1. There would be a statistically significant difference in disease characteristics of participants prescribed M-IE and LVR compared to participants not prescribed M-IE and LVR.
2. There would be a statistically significant difference in the rates of decline of SNIP, SVC percent predicted, PCF, and ALSFRS-R of participant's prescribed M-IE and LVR compared to participants not prescribed M-IE and LVR.
3. There would be a statistically significant difference in the number of chest infections and antibiotics used to treat them in participants prescribed M-IE and LVR to participants who were not prescribed M-IE and LVR.

4.4 Setting

This study took place at a tertiary Amyotrophic Lateral Sclerosis/Motor Neuron Disease (MND) Multidisciplinary Team (MDT) clinic in Beaumont Hospital, Dublin. All assessments were completed at the ALS/MND MDT clinic.

4.5 Ethical Considerations

Ethical approval was obtained from Beaumont Hospital Ethics Committee on August 13th 2015 (REC 1150) (Appendices 3 and 4). Ethical approval was subsequently sought from RCSI Research Ethics Committee on October 5th 2015 (Appendix 5).

A unique identifier number was assigned to each participant to insure confidentiality. The key to this code was known to the lead researcher only. The unique identifier numbers were stored on an encrypted excel document,

stored on an RCSI research laptop, protected by a password in the physiotherapy department in Beaumont Hospital. A hard copy with the unique identifier numbers was locked in a cabinet, accessible by a code in the physiotherapy department in Beaumont Hospital. Data collection forms were distinguished by unique identifier numbers. Data collected was kept in hard copy in a locked filing cabinet and soft copy format on the password protected laptop.

4.6 Sample Size

The sample size was based upon the data required for the planned regression analysis of the longitudinal data. The number of independent variables and the population size attending the Beaumont Hospital of ALS/MND MDT clinic were considered. The independent variables identified were site of onset, age, gender, time from diagnosis to study entry and time between each assessment.

Green (1991) states that a sample size of $n \geq 50 + 8m$, where m is the number of independent variables, is adequate for the testing of multiple correlations, while $n \geq 104 + m$ is adequate for testing individual predictors. Therefore a sample size of 109 was calculated.

4.7 Participants

4.7.1 Identifying Participants

Potential participants were identified at the ALS/MND MDT clinic in Beaumont Hospital. The diagnosis of ALS was made by the Consultant Neurologist according to the El Escorial Criteria (Brooks et al., 2000) (Chapter 2.3.1.6).

4.7.2 Inclusion and Exclusion Criteria

Potential participants were approached if they 1) had a diagnosis of ALS according to the El Escorial criteria, 2) could participate for the study duration and 3) could provide informed consent. Potential participants were excluded if they 1) were diagnosed with frontal temporal dementia or 2) could not

understand English. Inclusion and exclusion criteria were evaluated by the lead researcher by reviewing the potential participant's medical chart.

4.7.3 Recruitment

Recruitment commenced on August 27th 2015 and ended on 31st March 2016. The gatekeeper, a member of the ALS/MND team approached consecutive potential participants. An information leaflet (Appendix 6) was provided and the lead researcher was introduced. Aims, objectives, risks and ethical considerations were verbally outlined by the lead researcher if the individual expressed an interest in participating. Withdrawal from the study at any time without affecting their care was permitted and explained to the potential participant. A cooling off period was given during which time potential participants consulted with family members and carers, read the information leaflet and asked questions. Written informed consent was obtained from participants when they agreed to participate in the presence of the lead researcher (Appendix 7).

4.8 Assessments

The following assessments were measured by the lead researcher at each clinic visit following recruitment to the study. The assessment procedures took approximately 20 minutes to complete.

4.8.1 Demographics

Participant demographics were collected. This included gender, age, height, date of symptom onset, date of diagnosis, initial symptoms, site of onset, El Escorial criteria and past medical history. The ALS/MND register and the participant's medical chart were used to obtain this information.

4.8.2 Respiratory Measures

The respiratory tests were completed in the following order: SNIP, SVC, PCF. Self-reported chest infection rate and antibiotic use was recorded at each clinic visit.

4.8.2.1 Sniff Nasal Inspiratory Pressure

SNIP was used to assess respiratory muscle strength (Chapter 3.3.2.2). SNIP was measured by a MicroRPM respiratory pressure meter (Carefusion, Sword Medical, Blanchardstown, Dublin 15) (Figure 4.1). The correct nasal probe size (three or four) was ascertained by inserting it into the participant's nostril and the participant sniffed while the lead researcher occluded their opposite nostril. The correct nasal probe size was selected when there was no leakage around the nasal probe.

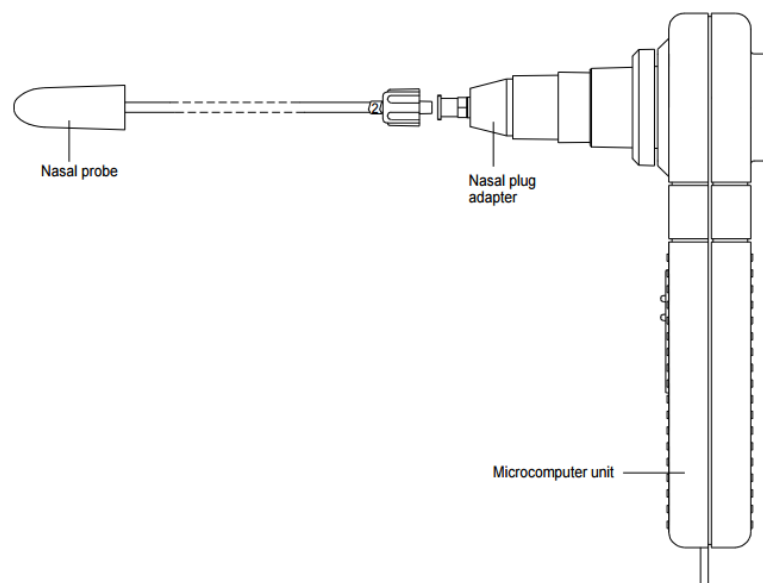


Figure 4.1: MicroRPM Respiratory Pressure Meter

The procedure for SNIP assessment was performed according to the European Network to Cure ALS (ENCALS) standard operating procedure for respiratory measurements (Appendix 1). Participants were seated with a closed mouth, the nasal probe was inserted and they were instructed to breathe normally. At the end of a normal tidal expiration they were instructed to perform a short, sharp maximal sniff with as much effort as possible through the open nostril. The machine was reset and a rest interval of 30 seconds was provided between each test. A minimum of ten attempts were performed. The test ended when there was no further increase in pressure. The highest reading was recorded in centimetres of water (cmH₂O).

4.8.2.2 Slow Vital Capacity

Vital Capacity in the form of Slow Vital Capacity (SVC) (Chapter 3.2.1) measured overall respiratory function. SVC is the maximum volume of air that can be inspired or expired from a relaxed manoeuvre (Hough, 2013). A MicroLab spirometer (36-ML3500- MK8, Sword Medical, Blanchardstown, Dublin 15) measured SVC (Figure 4.2).



Figure 4.2: MicroLab (36-ML3500- MK8, Sword Medical, Blanchardstown, Dublin 15).

A three litre syringe was used to calibrate the spirometer prior to data collection (Figure 4.3). Calibration is a quality control procedure that calculates the relationship between the flow or volume of air that is determined by the sensor and the actual volume of air (Miller et al., 2005). The calibration of the spirometer ensured an accurate and repeatable volume standard. The calibration syringe and the spirometer were allowed to adjust to room temperature for a minimum of 20 minutes prior to calibration. The calibration was performed at slow, moderate and fast air flow rates. The calibration check was successful if the volume recorded was within 3% of the known volume i.e. 2.01 -3.09 litres. The calibration verifications were printed and recorded.



Figure 4.3: A 3 Litre Calibrating Syringe

ENCALS standard operating procedure for respiratory measurements (Appendix 1) was followed to perform SVC. An oronasal facemask was used to prevent air leakage from the mouth. A maximum inhalation followed immediately by a relaxed maximum exhalation was performed in a seated position. Verbal cues and prompts were provided to encourage and ensure correct technique.

A minimum of three and a maximum of five manoeuvres were performed. The following criteria indicated the end of a test 1) the two highest readings had a variability of less than 250 millilitre (ml) or the two highest readings had a variability of less than 10% if the SVC was less than 100ml 2) participants became fatigued and they could not perform further assessments (Miller et al., 2005). The highest score was recorded. If the participants failed to meet the first criteria, the highest score recorded was taken. SVC was recorded in litres and expressed as a percentage of the predictive normal values. The European Coal and Steel Community (ECCS) reference values and the combined reference equations from the 1993 European Respiratory Society publication were used (Quanger et al., 1993).

4.8.2.3 Peak Cough Flow

Peak Cough Flow (PCF) is the peak flow generated with a cough through a peak flow meter (Bott et al., 2009) (Chapter 3.4.3). PCF was measured using a Wright Peak Flow Meter (Figure 4.4) connected to an oronasal mask. Participants inhaled to a maximum capacity and then forcibly coughed through the oronasal facemask in a seated position. A minimum of six measurements were taken until at least three reproducible manoeuvres with a variability of less than 10% was achieved. The maximum score was recorded in litres per minute (L/min). A score of less than 60 was recorded as 0 L/min and a score of 880 L/min was recorded as 881 L/min (Bach et al., 2006).



Figure 4.4: Wright Peak Flow Meter

4.8.3 Physical Function

4.8.3.1 Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised

The Amyotrophic Lateral Sclerosis Functional Rating Scale Revised (ALSFRS-R) was then completed (Chapter 3.5.1). The ALSFRS-R assessed participants' self-reported levels of function in their home (Appendix 2). The ALSFRS-R was carried out by the lead researcher according to ENCALS standard operating procedure (Appendix 8). Each participant answered the 12 questions. They compared their current symptoms to their normal function prior to symptom onset. The participants were not prompted unless the

participant's response did not correspond with their clinical presentation. If this scenario occurred the list of responses was read out and the participant's response was explored further. Participants with severe bulbar involvement used non-verbal communication devices such as hand writing or text to speech programmes. If the above means of communication were not possible, the participant's family member or carer assisted. This was marked out of a total score of 48.

4.8.4 Outcome

Outcome was determined by 1) the number of chest infections and antibiotics used during the study period 2) the number of participants alive at study conclusion. The lead researcher asked each participant 1) 'Have you had a chest infection since your last visit to the ALS/MND MDT clinic?' If the participant answered yes a second question 2) 'Did you require antibiotics for the treatment of this chest infection?' was asked. The answers were documented in yes/no and numerical format. A letter (Appendix 9) was also sent to the participant's General Practitioner (GP) to cross reference chest infection frequency and antibiotic use.

4.9 Prescription

This was an observational study and did not influence the prescription of M-IE and LVR. Therefore the physiotherapists prescribed M-IE and LVR at the ALS/MND MDT clinic as indicated by standard clinical criteria to all suitable participants. Two physiotherapists work in the ALS/MND service, with one physiotherapist attending each ALS/MND MDT clinic. Both Physiotherapists have extensive experience working with ALS patients of between seven and 10 years.

The consultant neurologist or a neurology registrar referred the participant to the physiotherapist if difficulty clearing secretions was reported. If M-IE or LVR was prescribed to a participant a data collection form (Appendix 10) was completed by the prescribing physiotherapist. The data collection form comprised of the device prescribed, subjective symptoms, SNIP, SVC percent predicted, PCF and ALSFRS-R. The subjective symptoms are outlined in Table 4.1.

Table 4.1: Subjective Symptoms at Prescription

Dyspnoea
Productive Cough
Ineffective cough
Audible secretions
Reported secretion retention
Reported inability to clear secretions
Fatigue with coughing

4.10 Statistical Methods

A statistician was consulted with regard to the analysis plan. Data was entered into Microsoft Excel and analysed using SPSS (IBM SPSS Statistics 23) and R Studio (1.0.44). All data was assessed for normality using visual inspection of normal distribution curves and the Shapiro-Wilk test (Pallant, 2013). Normally distributed data was summarised using means and Standard Deviation (SD). Non-parametric data was summarised using medians and ranges. Independent two sample t-tests were conducted to compare differences between normally distributed variables and Mann-Whitney U tests were conducted to compare differences between non-parametric variables. Chi-square tests were used to assess the relationship between two categorical variables. Demographic data was summarised using summary statistics and categorical frequencies. Summary statistics were calculated for all outcome measures.

A multilevel repeated measures model for unbalanced follow up and to account for missing data (Cnaan et al., 1997) was used to analyse longitudinal measurements of SNIP, SVC percent predicted, PCF and ALSFRS-R. This model also calculated the average values of SNIP, SVC percent predicted, PCF and ALSFRS-R for participants prescribed M-IE and LVR compared to participants not prescribed a device. A second model

calculated the changes of SNIP, PCF, SVC Percent Predicted and ALSFRS-R over time between participants prescribed a device and not prescribed a device. Independent variables included in the analysis were site of onset, age, gender, time from diagnosis to study entry and time between each respiratory assessment.

Descriptive statistics were used to calculate the number of chest infections and the number of antibiotics prescribed reported to treat them. Mann-Whitney U tests were used to compare the number of chest infections of participants prescribed M-IE and LVR to participants who were not prescribed M-IE and LVR. Summary statistics were calculated for SNIP, SVC percent predicted, PCF and ALSFRS-R at the time of M-IE and LVR prescription. Data was further stratified into site of onset of ALS and type of device to determine differences between measurements.

4.11 Conclusion

This chapter has outlined the design of the study, the selection of participants, the procedure of the assessments and the acquirement and analysis of the data. Results of the study are presented in Chapter 5.

Chapter 5: Respiratory Measurements, Physical Function and Airway Clearance Device Prescription over One Year in Amyotrophic Lateral Sclerosis: Results

5.1 Introduction

The prospective longitudinal and observational cohort study had two aims. The first aim was to measure respiratory muscle strength, function and morbidity, cough strength, physical function and outcome in an Irish Amyotrophic Lateral Sclerosis (ALS) cohort. The second aim was to examine prescription practices in relation to Mechanical Insufflation Exsufflation (M-IE) and Lung Volume Recruitment (LVR) devices and to compare the above characteristics in those prescribed such devices and those who were not.

The objectives were:

1. To prospectively measure the changes in SNIP, SVC percent predicted, PCF, and ALSFRS-R over one year in a cohort of ALS patients
2. To measure the frequency of M-IE and LVR prescription
3. To identify the characteristics of participants at the time of M-IE and LVR prescription. This included time from diagnosis, site of onset, SNIP, SVC percent predicted, PCF and ALSFRS-R and respiratory symptoms
4. To compare the characteristics of the participants prescribed M-IE and LVR to participants not prescribed M-IE and LVR
5. To compare the rates of decline of SNIP, SVC percent predicted, PCF, and ALSFRS-R of participants prescribed M-IE and LVR to participants who were not prescribed M-IE and LVR.
6. To compare the number of chest infections reported and the number of antibiotics prescribed to treat them in all participants
7. To compare the number of chest infections and antibiotics used to treat them in participants prescribed M-IE and LVR to participants who were not prescribed M-IE and LVR
8. To determine the number of participants alive at study conclusion

The hypotheses were:

1. There would be a statistically significant difference in disease characteristics of participants prescribed M-IE and LVR compared to participants not prescribed M-IE and LVR.
2. There would be a statistically significant difference in the rates of decline of SNIP, SVC percent predicted, PCF, and ALSFRS-R of participant's prescribed M-IE and LVR compared to participants not prescribed M-IE and LVR.
3. There would be a statistically significant difference in the number of chest infections and antibiotics used to treat them in participants prescribed M-IE and LVR to participants who were not prescribed M-IE and LVR.

5.2 Participants

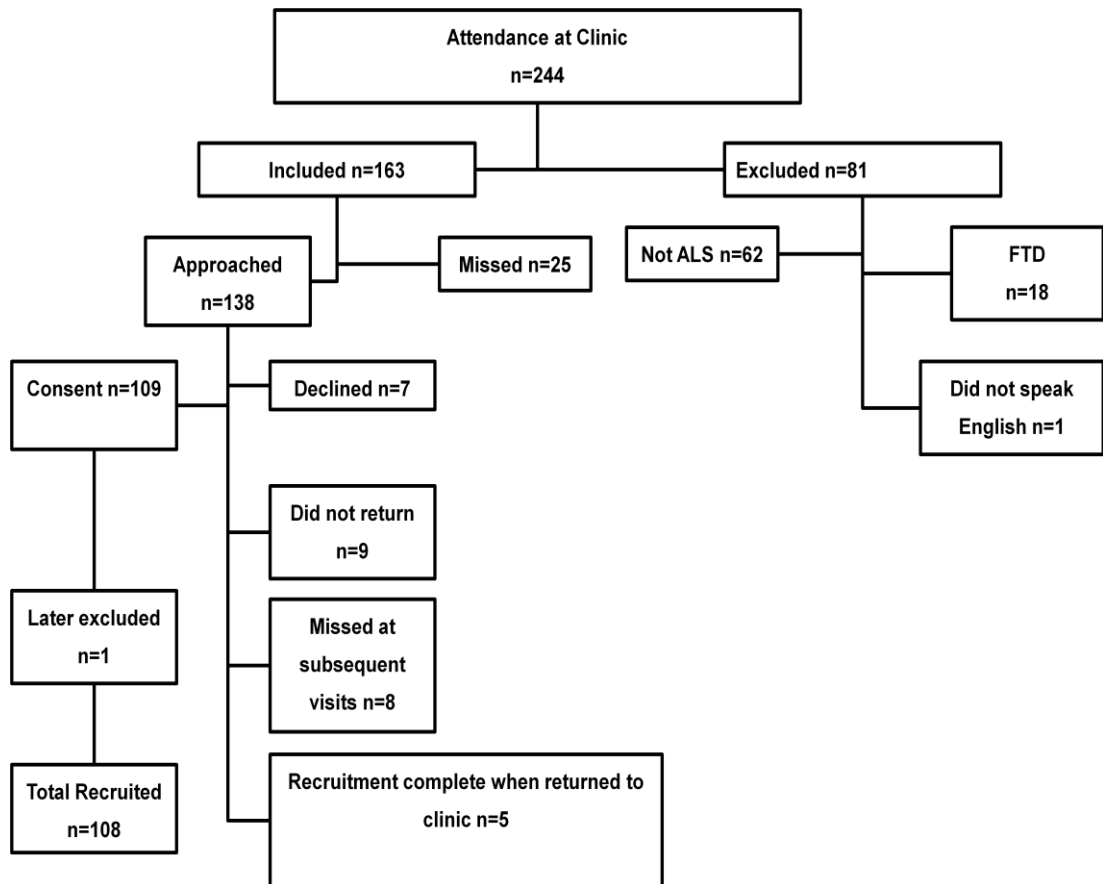
One hundred and nine participants were recruited during the study period which commenced on the 27th August 2015 and ceased on the 31st March 2016. During the recruitment phase 244 individual patients attended the Amyotrophic Lateral Sclerosis/Motor Neuron Disease (ALS/MND) Multidisciplinary Team (MDT) clinic. Figure 5.1 displays the patients that attended clinic and reason for inclusion or exclusion.

One hundred and sixty three patients were suitable for inclusion to the study during the recruitment phase. Twenty five patients that attended the ALS/MND MDT clinic were potentially suitable but could not be approached due to time constraints of the gate keeper at the ALS/MND MDT clinic. One hundred and thirty eight participants were approached by a member of the MND team. Twenty-nine patients were approached at the clinic but were not enrolled as they declined (n=7), did not return to clinic (n=9), they were missed at subsequent clinics due to time constraints (n=8) of the lead researcher or the recruitment process was complete when they returned to clinic (n=5).

5.2.1 Excluded Participants

Eighty one participants were excluded because they did not have a diagnosis of ALS (n=62), they had frontotemporal dementia (n=18) or they did not speak English (n=1).

Of the 109 participants recruited, one was later excluded. At the time of recruitment this participant had a diagnosis of ALS but during the study period their diagnosis was changed to possible dystonia by the consultant neurologist. A total of 108 participants were therefore included in the final analysis.



FTD=Frontotemporal Dementia

Figure 5.1: Flow of Participants

5.3 Missing Data

Nine SNIP and SVC; five ALSFRS-R and four PCF assessments were not completed over the one year study. Reasons the assessments were not completed are outlined in Table 5.1.

Table 5.1: Missing Data

Measurement	Number of Missed Measurements	Reasons for Missed Measurements	n
SNIP (cmH ₂ O)	9	Unwell Trigeminal nerve pain	6 3
PCF (L/min)	4	Unwell Left for transport Fatigue	2 1 1
SVC (%)	9	Unwell Left for transport Fatigue	7 1 1
ALSFRS-R (x/48)	5	Unwell	5

SNIP=Sniff Nasal Inspiratory Pressure, cmH₂O=centimetres of water, PCF=Peak Cough Flow, L/min=Litres per minute, SVC%=Slow Vital Capacity percent predicted, %=percent, ALSFRS-R=Amyotrophic Lateral Sclerosis Functional Rating Scale Revised, n=number,

5.4 Description of Study Group

The study sample consisted of 71 males (65.7%) and 37 females (34.3%). The mean age of the cohort at study entry was 62.1±11.5 years. The mean age of symptom onset was 59.0±11.61 years and the mean age at diagnosis was 60.16±11.91 years. Time since diagnosis to study entry was a median of 8.5 months with a range of 0 – 90 months. Details of participant demographics are described are in Table 5.2 and Table 5.3.

Table 5.2: Demographics of Participants

	Male (n=71)	Female (n=37)	Difference Between Male and Female	
	Mean (SD)	Mean (SD)	Diff (95% CI diff)	p-value
Age at Study Entry (Years)	60.3 (11.9)	65.4 (9.9)	5.2 (0.63,9.67)	0.03
Age at Diagnosis (Years)	58.97 (11.84)	62.43 (11.86)	3.46 (-1.3,8.22)	0.15
	Median (Range)	Median (Range)	Median Diff (CI of Diff)	
Time since Diagnosis to Study Entry (Months)	8 (0,90)	10 (0,71)	2 (4,7.5)	0.55*

n=number, SD=standard deviation, 95% CI diff=95% confidence interval of the difference between the two groups, Median Diff=difference of median *=Mann Whitney U Test

Table 5.3: Demographics Stratified into Bulbar and Spinal Onset ALS

	Spinal (n=85)	Bulbar (n=23)		
	Mean (SD)	Mean (SD)	Diff (95% CI diff)	p-value
Age at Study Entry (Years)	62.22 (11.71)	61.39 (10.75)	0.83 (-4.53,6.2)	0.76
Age at Diagnosis (Years)	60.11 (12.2)	60.35 (11.03)	-0.24 (-5.82,5.33)	0.93
	Median (Range)	Median (Range)	Median Diff (CI of Diff)	
Time Since Diagnosis (Months) to Study Entry	9.0 (0,90)	8.0 (0,35)	1.0 (6,10.5)	0.46*

n=number, SD=standard deviation, 95% CI diff=95% confidence interval of the difference between the two groups, Median Diff=difference of median, *=Mann Whitney U Test

5.5 Amyotrophic Lateral Sclerosis Characteristics

All participants recruited were diagnosed with ALS by the El Escorial Criteria (Brooks et al., 2000). First reported symptoms by spinal onset participants are shown in Figure 5.2 with upper and lower limb weakness being the most common first symptoms reported. The first symptoms experienced by all twenty three (100%) bulbar participants were swallowing and speech difficulties.

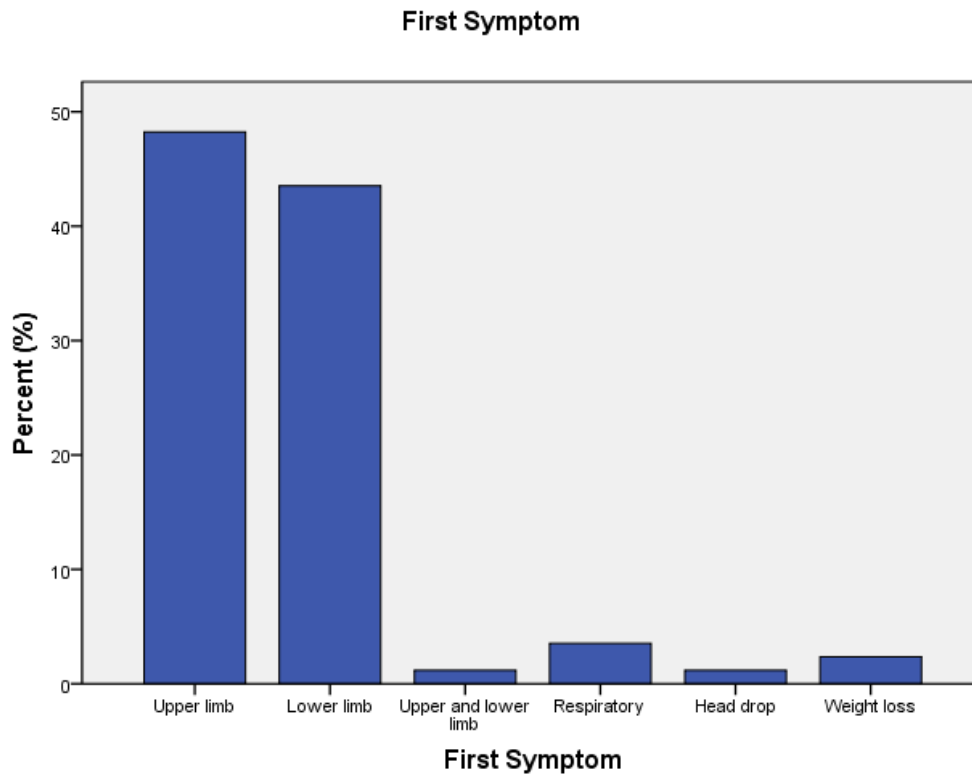


Figure 5.2: First Symptoms Reported by Spinal Onset ALS Participants

5.6 Baseline Measurements

Baseline measurements are described in Table 5.4. SNIP measured inspiratory muscle strength. Two participants did not complete SNIP at baseline. Forty-six participants had a SNIP less than 40cmH₂O. Cough strength was assessed by PCF. Data were missing for four participants at study entry. A total of 16 participants had a PCF less than 160L/min. VC measured by SVC was completed by 104 participants at study entry. A total of 84 participants had an SVC percent predicted greater than 50%. Function measured with the ALSFRS-R was completed by all participants at baseline. Sixty-seven participants had a score less than 38 out of 48 at study entry.

Table 5.4: Baseline Measurements

	n	Median (Range)
SNIP (cmH₂O)	106	45 (5,122)
SVC%	104	81.0 (20,124)
ALSFRS-R (x/48)	108	36 (8,47)
		Mean (SD)
PCF (L/min)	104	346.44 (153.27)

SNIP=Sniff Nasal Inspiratory Pressure, cmH₂O=centimetres of water, SVC%=Slow Vital Capacity percent predicted, %=percent, ALSFRS-R=Amyotrophic Lateral Sclerosis Functional Rating Scale Revised, PCF=Peak Cough Flow, L/min=Litres per minute, SD=Standard Deviation

Male participants had a significantly higher PCF at baseline compared to females ($p<0.0001$). There were no significant differences in SNIP, SVC percent predicted and ALSFRS-R baseline measurements between males and females ($p>0.05$) (Table 5.5).

Spinal onset ALS participants had a significantly higher PCF than bulbar onset ALS participants. There were no significant differences in SNIP, SVC percent predicted and ALSFRS-R baseline measurements between spinal and bulbar onset ALS ($p>0.05$) (Table 5.6).

Table 5.5: Male and Female Baseline Measurements

	Male		Female		Difference Between Male and Female	
	n	Mean (SD)	n	Mean (SD)	Diff (95% CI diff)	p-value
PCF (L/min)	67	392.69 (151.70)	37	262.7 (117.63)	129.98 (-187.11,-72.85)	<0.0001
		Median (range)		Median (range)	Median Diff (CI of Diff)	
SNIP (cmH₂O)	69	53(5,122)	37	37(5,102)	16 (26.5,37)	0.67*
SVC% (%)	67	81 (20,115)	37	84.0 (23,124)	3(42,49.5)	0.77*
ALSFRS-R (x/48)	71	36 (8,47)	37	37 (16,46)	1(18.5,21)	0.60*

n=number, SD=standard deviation, 95% CI diff=95% confidence interval of the difference between the two groups, Median

Diff=difference of median, *=Mann Whitney U Test, PCF=Peak Cough Flow, L/min=Litres per minute, SNIP=Sniff Nasal Inspiratory

Pressure, cmH₂O=centimetres of water, SVC%=Slow Vital Capacity percent predicted, %=percent, ALSFRS-R=Amyotrophic Lateral

Sclerosis Functional Rating Scale Revised

Table 5.6: Spinal and Bulbar Baseline Measurements

	Spinal		Bulbar		Difference Between Spinal and Bulbar	
	N	Mean (SD)	n	Mean (SD)	Diff (95% CI diff)	p-value
PCF (L/min)	81	366.79 (149.56)	23	274.78 (147.52)	92.01 (22.12,161.89)	0.01
		Median (range)		Median (range)	Median Diff (CI of Diff)	
SNIP	83	43.0 (5,122)	23	50.0 (5,117)	-7 (32,46)	0.08*
SVC%	81	83 (21,124)	23	78.0 (20,108)	5 (56,81)	0.39*
ALSFRS-R	85	36 (13,45)	23	36 (8,47)	0 (30,36)	0.83*

n=number, SD=standard deviation, 95% CI diff=95% confidence interval of the difference between the two groups, Median Diff=difference of median, *=Mann Whitney U Test, PCF=Peak Cough Flow, L/min=Litres per minute, SNIP=Sniff Nasal Inspiratory Pressure, cmH₂O=centimetres of water, SVC%=Slow Vital Capacity percent predicted, %=percent, ALSFRS-R=Amyotrophic Lateral Sclerosis Functional Rating Scale Revised

5.6.1 Respiratory Muscle Strength and Function, Cough Strength and Physical Function

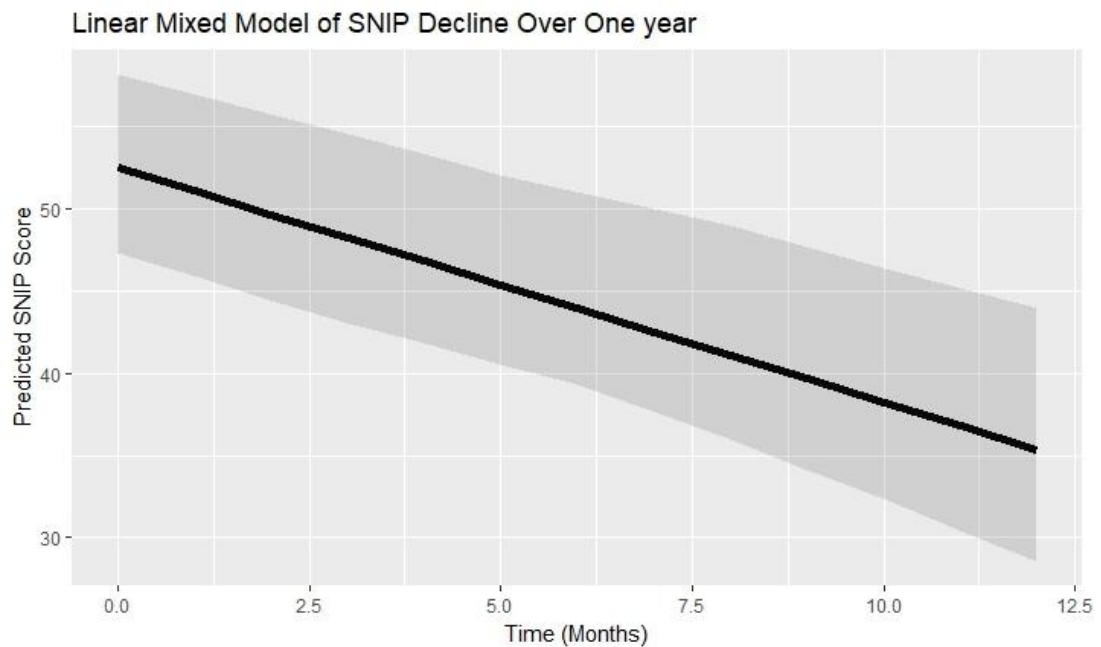
A total of 338 SNIP, 343 PCF, 338 SVC and 342 ALSFRS-R assessments were completed in 108 participants during the study period. Participants were reviewed by the lead researcher an average of 3.12 times, ranging from one to six times. The number of observations, rate of decline per year, standard error, percentage rate of change per year and level of significance are shown in Table 5.7.

Table 5.7: Respiratory Measurements and ALSFRS-R Rates of Decline over the Study Period

	Rate of Decline per Year	Number of Observations	Standard Error	p-value	Percentage Rate of Change per Year
SNIP (cmH₂O)	18.72	338	0.27	<0.001	37.1%
PCF (L/min)	124.84	343	1.54	<0.001	38.41%
SVC percent predicted (%)	17.49	338	0.30	<0.001	23.51%
ALSFRS-R (x/48)	9.62	342	0.08	<0.001	29.64%

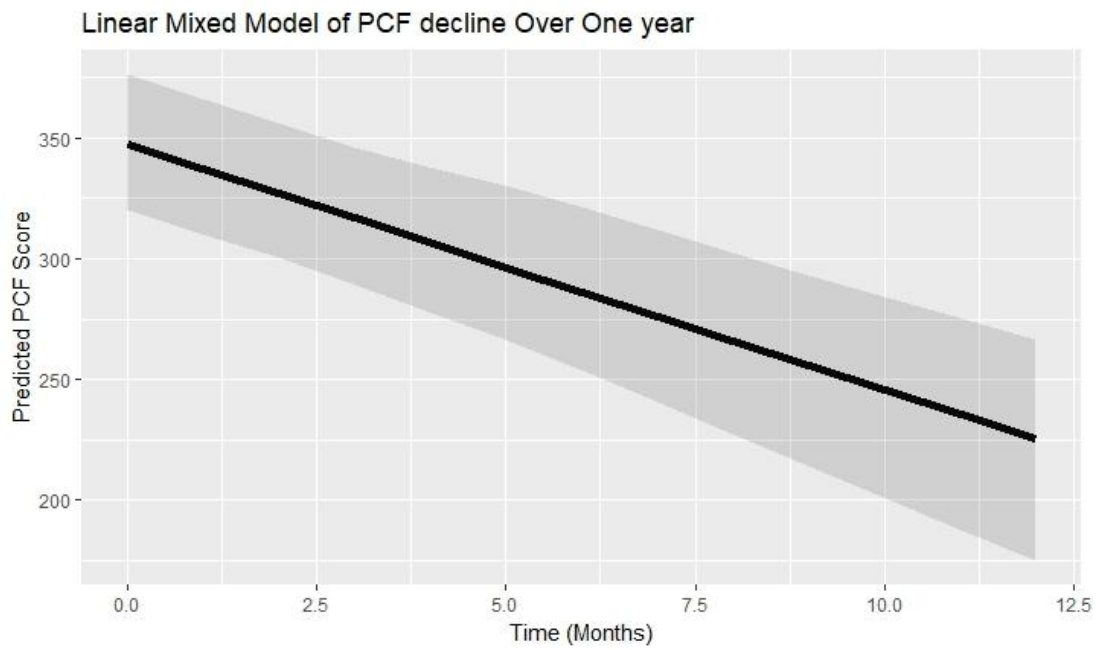
SNIP=Sniff Nasal Inspiratory Pressure, cmH₂O=centimetres of water, PCF=Peak Cough Flow, L/min=Litres per minute, SVC%=Slow Vital Capacity percent predicted, %=percent, ALSFRS-R=Amyotrophic Lateral Sclerosis Functional Rating Scale Revised

Plots of SNIP (Figure 5.3), PCF (Figure 5.4), SVC percent predicted (Figure 5.5) and ALSFRS-R (Figure 5.6) are illustrated below. The plots illustrate the rate of decline of each outcome measure over the one year study period starting at study entry.



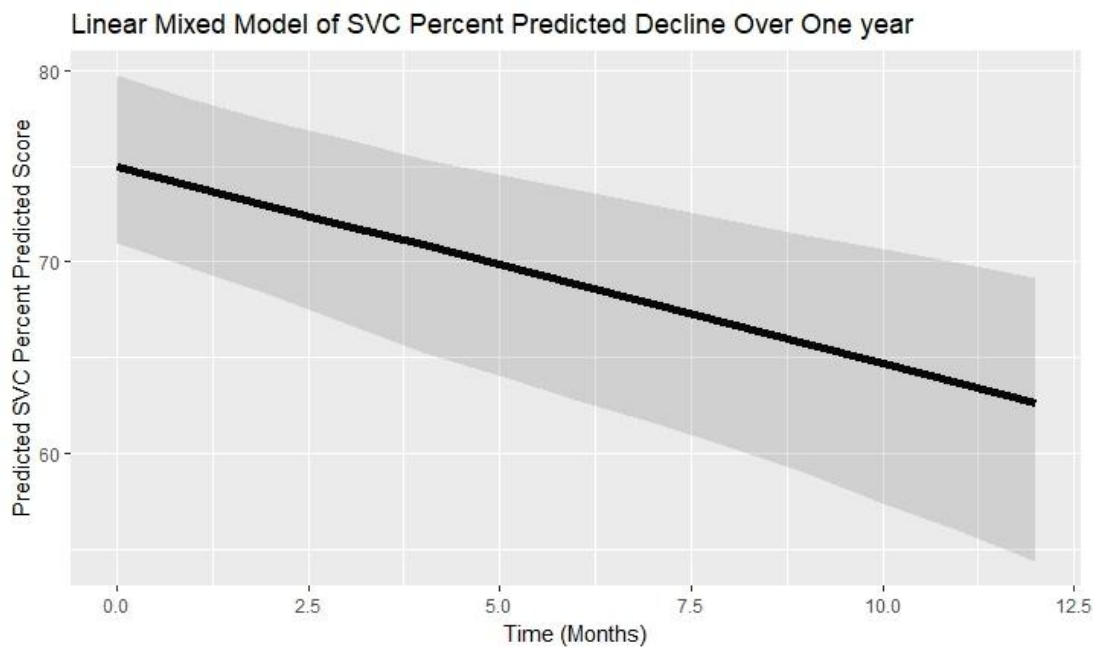
SNIP=Sniff Nasal Inspiratory Pressure

Figure 5.3: Linear Mixed Model of SNIP Decline Over One Year



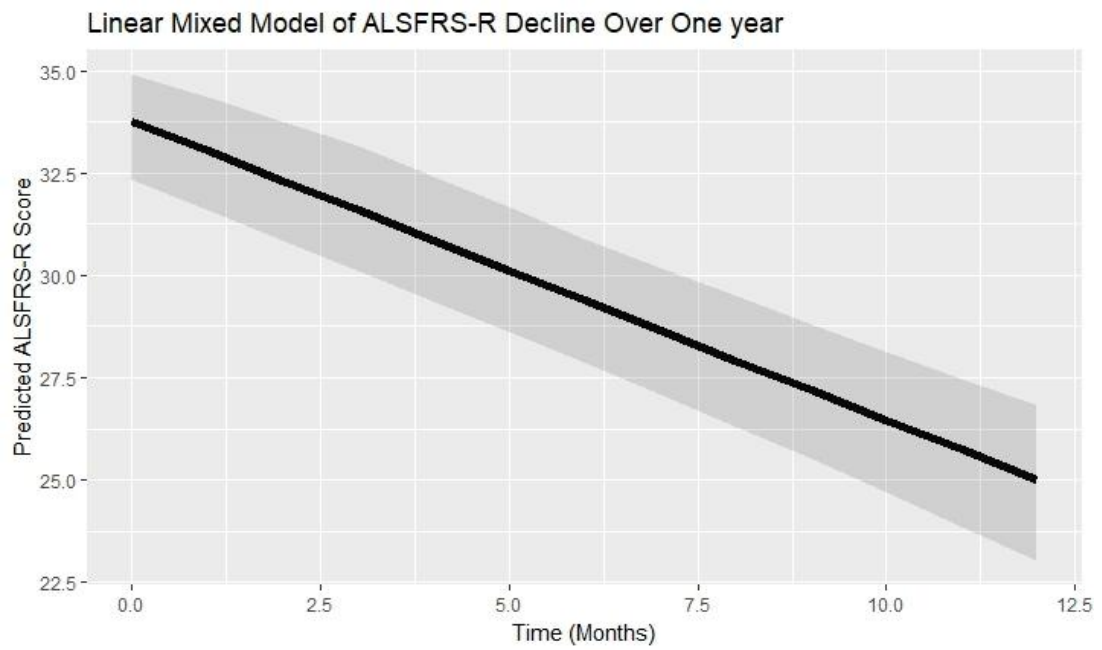
PCF=Peak Cough Flow

Figure 5.4: Linear Mixed Model of PCF Decline Over One Year



SVC=Slow Vital Capacity

Figure 5.5: Linear Mixed Model of SVC Percent Predicted Decline Over One Year



ALSFRS-R=Amyotrophic Lateral Sclerosis Functional Rating Scale Revised

Figure 5.6: Linear Mixed Model of ALSFRS-R Decline Over One Year

5.7 Mortality

Eighty-seven (80.56%) participants were alive and 21 (19.44%) participants had passed away at study conclusion.

5.8 Chest Infection Frequency and Antibiotic Use

Fifty-six chest infections were self-reported by 32 participants. Chest infection incidence among the participants was 29.63% (32/108). Antibiotics treated chest infections on 40 occasions. Antibiotic rate among participants that self-reported a chest infection was 71.43% (40/56).

There was a 52.8% (n=57) response rate from General Practitioners (GP)s regarding chest infection frequency and antibiotic use. Forty seven chest infections were reported among 28 participants. GP reported chest infection rate was 25.93% The GPs reported that 41 antibiotics were prescribed for the forty seven chest infections. The rate of antibiotics to treat the GP reported chest infections among participants was 87.23%.

A Chi-square test for independence (with Yates Continuity Correction) indicated a significant association between the number of self-reported chest infections and the proportion of GPs who responded and reported a chest infection, $\chi^2 (1, n=57), =4.16, p=0.04, \phi=0.31$ (Pallant, 2013). When this was analysed further into the exact total of number of chest infections by self-report and GP report methods, of the 57 GPs who responded, there was 50.9% (n=29) agreement between the number of chest infection reported by participants and the number of chest infections reported by GPs. Table 5.8 describes the self-report and GP report chest infections and percentage agreement between the two methods.

Table 5.8: Self-report and GP Report Chest Infections and Percentage Agreement between the Two Methods

Number of Chest Infections	Self-Report	GP Report	Number of Agreement	Percentage Agreement (%)
0	73	29	23	40.35
1	26	15	5	8.77
2	4	10	0	0
3	1	1	0	0
4	3	1	1	1.75
5	0	1	0	0
6	1	0	0	0

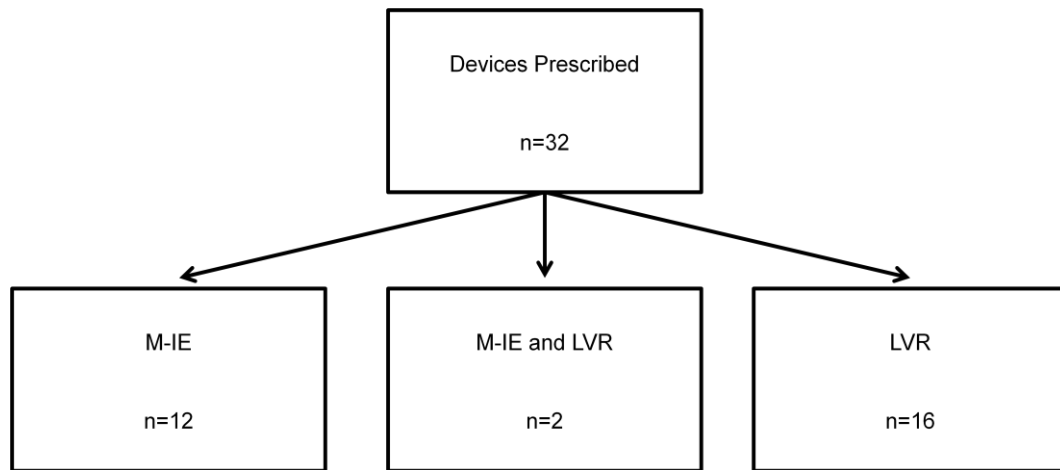
%=percent

5.9 Prescription

5.9.1 Frequency of M-IE and LVR prescription

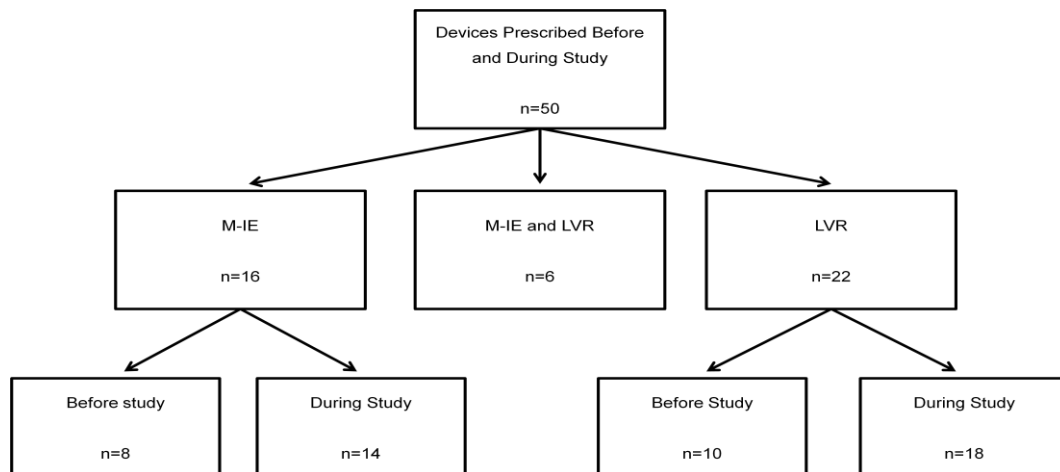
Thirty-two devices were prescribed to 30 (27.78%) of the 108 participants during the study period (Figure 5.7 and Figure 5.8). Of these 30 participants, two received both LVR and M-IE; four had in addition received a device prior to the study period. Of the 108 participants, 18 (16.67%) were prescribed a device before the study and 60 (55.56%) participants were not prescribed a device before or during the study period.

The rate of prescription of a device during the one year study period was 29.63% (32/108). Slightly more LVR devices (18, 56.3%) than M-IE devices (14, 43.8%) were prescribed. The frequency of LVR and M-IE prescription during the study period was 16.67% (18/108) and 12.96% (14/108) respectively in the recruited participants. Additionally, 18 participants were prescribed a device prior to the study period. At study conclusion, 48 (51.84%) participants had been prescribed a device before or during the study period.



M-IE=Mechanical Insufflation Exsufflation, LVR=Lung Volume Recruitment

Figure 5.7: Flow Chart of the Prescription of Devices During Study Period



M-IE=Mechanical Insufflation Exsufflation, LVR=Lung Volume Recruitment

Figure 5.8: Flow Chart of the Prescription of Devices Before and During Study Period

5.9.2 Characteristics of Participants not prescribed M-IE and LVR

Sixty participants were not prescribed a device. The mean age of these 60 participants was 60.02 ± 12.84 years. The median time from diagnosis to study entry was 7.5 (0,90) months. Age and time from diagnosis to study entry for males and females are described in Table 5.9 and site of onset in Table 5.10.

Table 5.9: Demographics of Participants Not Prescribed a Device

	Male		Female		Difference Between Male and Female	
	N	Mean (SD)	n	Mean (SD)	Diff (95% CI diff)	p-value
Age (Years)	38	55.95 (13.06)	22	67.55 (8.6)	11.6 (5.36,17.84)	0.03
		Median (Range)		Median (Range)	Median Diff (CI of Diff)	
Time from Diagnosis to Study Entry (months)	38	7.5 (0,96)	22	8.0 (4,81)	0.5 (3.5,8)	0.914*

n=number, SD=standard deviation, 95% CI diff=95% confidence interval of the difference between the two groups, Median Diff=difference of median, *=Mann Whitney U Test

Table 5.10: Demographics of Spinal and Bulbar Participants Not Prescribed a Device

	N	Spinal	n	Bulbar		
	49	Mean (SD)	11	Mean (SD)	Diff (95% CI diff)	p-value
Age (Years)		60.6 (12.98)		58.46 (12.66)	2.14 (-6.5,10.77)	0.62
		Median (Range)		Median (Range)	Median Diff (CI of Diff)	
Time from Diagnosis to Study Entry (months)		8 (0,90)		6 (0,35)	2 (4,12)	0.26*

n=number, SD=standard deviation, 95% CI diff=95% confidence interval of the difference between the two groups, Median Diff=difference of median, *=Mann Whitney U Test

5.9.3 Characteristics of Participants at the Time of M-IE and LVR prescription

M-IE and LVR were prescribed a median of 11 (1,60) months after diagnosis. Age at study entry for these 30 participants was 63.0 ± 10.2 years. Devices were prescribed to 25 spinal and five bulbar ALS participants (Table 5.11 and Table 5.12). M-IE was prescribed to nine spinal participants and to five bulbar participants. LVR was prescribed to 16 participants.

Table 5.11: Demographics of Participants Prescribed a Device

	Male		Female		Difference Between Male and Female	
	n	Mean (SD)	n	Mean (SD)	Diff (95% CI diff)	p-value
Age at Study Entry (Years)	20	64.25 (9.34)	10	60.5 (11.84)	-3.75 (-11.85,4.35)	0.35
		Median (Range)		Median (Range)	Median Diff (CI of Diff)	
Time since Diagnosis to Prescription (Months)	21	10.0 (2,60)	11	12.0 (1,32)	2 (4,12)	0.8*

n=number, SD=standard deviation, 95% CI diff=95% confidence interval of the difference between the two groups, Median Diff=difference of median, *=Mann Whitney U Test

Table 5.12: Demographics of Spinal and Bulbar Participants Prescribed a Device

	n	Spinal	n	Bulbar		
		Mean (SD)		Mean (SD)	Diff (95% CI diff)	p-value
Age at Study Entry (Years)	25	62.68 (10.43)	5	64.60 (9.86)	-1.92 (-12.30,8.47)	0.71
		Median (Range)		Median (Range)	Median Diff (CI of Diff)	
Time since Diagnosis to Prescription (Months)		10.5 (1,60)		14.0 (2,32)	3.5 (6,14)	0.87*

n=number, SD=standard deviation, 95% CI diff=95% confidence interval of the difference between the two groups, Median Diff=difference of median, *=Mann Whitney U Test

Respiratory measures and ALSFRS-R scores at the time of prescription are presented in Table 5.13. Participant respiratory measures and ALSFRS-R scores for participants prescribed two devices during the study period are included for each device. Five SNIP, SVC percent predicted and ALSFRS-R assessments were missing at the time of prescription. The SNIP, SVC percent predicted and ALSFRS-R were not performed at the time of prescription as the participants were reviewed by the prescribing physiotherapist only. On these five occasions, participants were not well enough to be assessed for additional assessments.

Table 5.13: Respiratory Measures and ALSFRS-R scores of Participants at the Time of M-IE or LVR Prescription

	Number of devices prescribed	Number of assessments measured	Mean (SD)
SNIP (cmH₂O)	32	27	31.96 (15.93)
PCF (L/min)	32	32	241.41 (133.23)
SVC% (%)	32	27	60.59 (21.82)
ALSFRS-R (x/48)	32	27	29.63 (7.2)

n=number, SD=standard deviation, SNIP=Sniff Nasal Inspiratory Pressure, cmH₂O=centimetres of water, PCF=Peak Cough Flow ,L/min=Litres per minute; SVC%=Slow Vital Capacity percent predicted, %=percent, ALSFRS-R=Amyotrophic Lateral Sclerosis Functional Rating Scale Revised

5.9.3.1 Differences between Participants Prescribed M-IE and LVR at the Time of M-IE and LVR Prescription

SNIP (p=0.05) and PCF (p=0.001) were significantly higher in participants prescribed LVR compared to M-IE (Table 5.14). SVC percent predicted (p=0.21) and ALSFRS-R (p=0.36) were also slightly higher in the participants prescribed LVR compared to M-IE but this was not significant. Time from diagnosis to the prescription of LVR compared to M-IE (p=0.52) was not significantly higher.

Table 5.14: Comparison of Respiratory Measurements and ALSFRS-R between M-IE and LVR Prescription

	M-IE		LVR		Difference Between M-IE and LVR	
	n	Mean (SD)	n	Mean (SD)	Diff (95% CI diff)	p-value
SNIP (cmH₂O)	12	25.25 (16.94)	15	37.33 (13.27)	12.08 (-24.05,-0.12)	0.05
PCF (L/min)	14	159.64 (123.61)	18	305 (104.39)	145.36 (-227.68,-63.03)	0.001
SVC% (%)	12	54.58 (22.80)	15	65.4 (20.50)	10.82 (-27.99,6.37)	0.21
ALSFRS-R (x/48)	12	28.17 (9.44)	15	30.8 (4.8)	-2.63 (-8.39,3.12)	0.36
		Median (Range)		Median (Range)	Median Diff (CI of Diff)	
Time since Diagnosis to Prescription (Months)	14	10.5 (2,37)	18	11.5 (1,60)	1.0 (4,12)	0.52*

n=number, M-IE=mechanical insufflation exsufflation, LVR=lung volume recruitment, SD=standard deviation, 95% CI diff=95% confidence interval of the difference between the two groups, SNIP=Sniff Nasal Inspiratory Pressure, cmH₂O=centimetres of water, PCF=Peak Cough Flow ,L/min=Litres per minute; SVC%=Slow Vital Capacity percent predicted, %=percent, ALSFRS-R=Amyotrophic Lateral Sclerosis Functional Rating Scale Revised, Median Diff=difference of median, *=Mann Whitney U Test

5.9.4 Respiratory Symptoms

The most common respiratory symptom reported to the prescribing physiotherapists by the participants at the time of M-IE and LVR prescription was an ineffective cough (80.60% (n=25)) (Figure 5.9). The least common symptom reported was audible secretions (16.10% (n=5)).

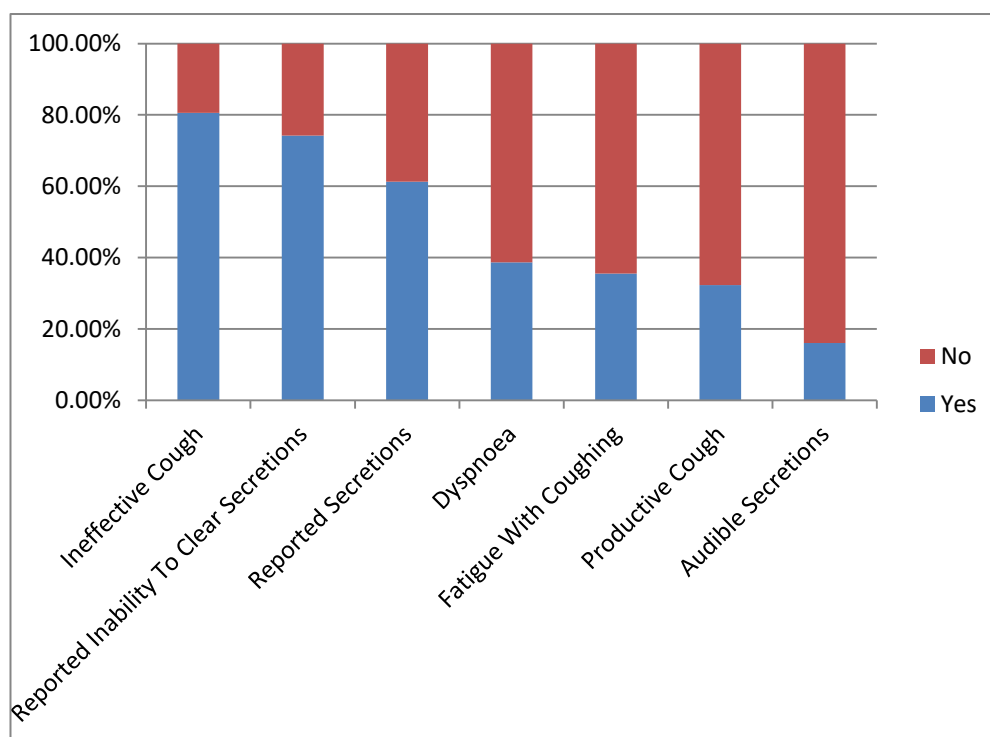


Figure 5.9: Bar Graph of Subjective Respiratory Symptoms at Time of Prescription of M-IE and LVR

An ineffective cough was more commonly reported by the participants prescribed M-IE compared to LVR (Figure 5.10). A reported inability to clear secretions was more commonly reported for the prescription of LVR compared to M-IE (Figure 5.11).

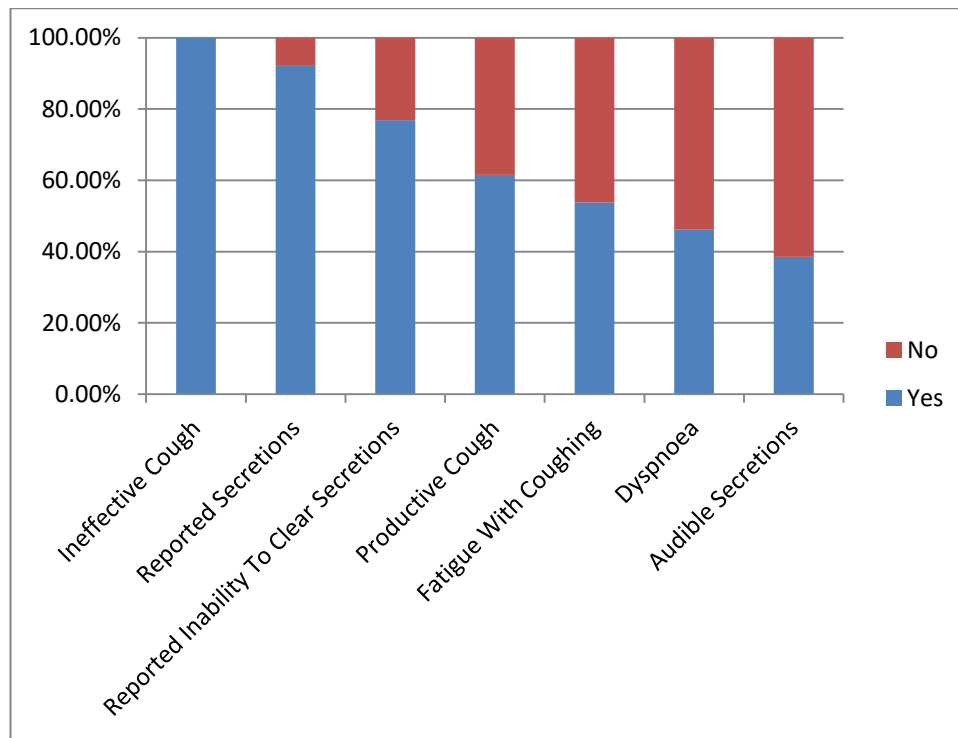


Figure 5.10: Bar Graph of Subjective Respiratory Symptoms at Time of Prescription for M-IE

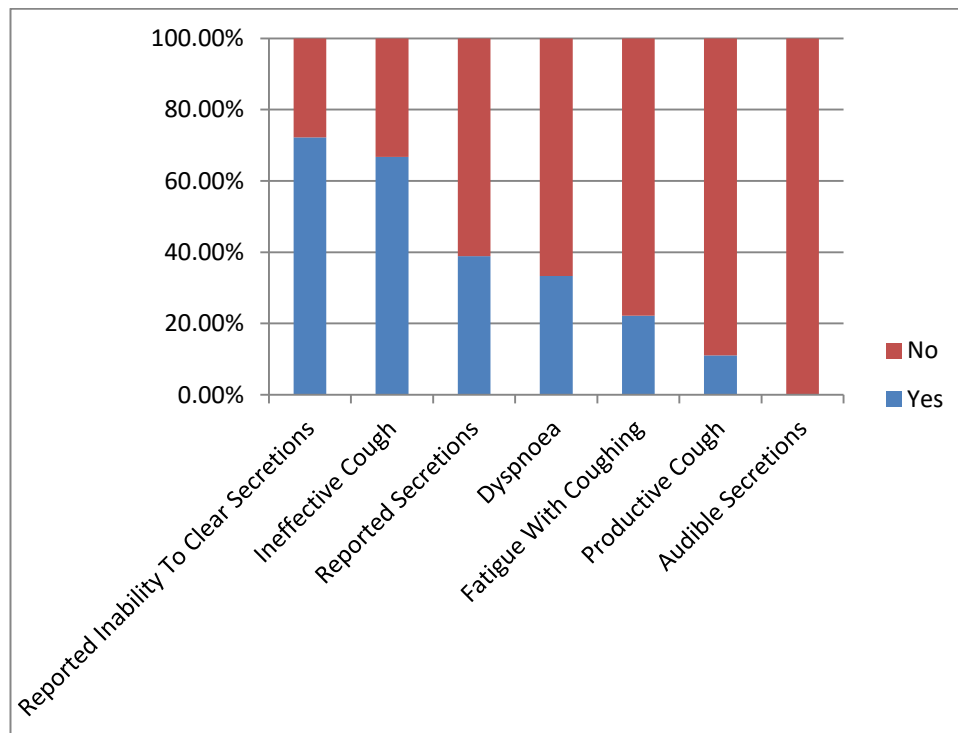


Figure 5.11: Bar Graph of Subjective Respiratory Symptoms at Time of Prescription for LVR

5.9.5 Differences between Spinal and Bulbar ALS Participants at the Time of M-IE and LVR Prescription

A Chi-square test for independence (with fisher-exact test) indicated no significant association between the site of onset ALS and the device prescribed, χ^2 (1, n=32), $p=0.06$, $\phi=-0.38$ (Pallant, 2013). PCF was significantly higher ($p=0.005$) in spinal compared to bulbar onset ALS participants at the time of prescription (Table 5.15). SNIP ($p=0.74$), SVC percent predicted ($p=0.31$) and ALSFRS-R ($p=0.28$) were not significantly higher in spinal compared to bulbar onset ALS participants. Time since diagnosis was also not significantly different in spinal and bulbar onset ALS participants ($p=0.87$).

Table 5.15: Spinal and Bulbar Respiratory Measures, ALSFRS-R Score and Time since Diagnosis to Prescription

	Spinal		Bulbar			
	n	Mean (SD)		Mean (SD)	Diff (95% CI diff)	p-value
SNIP (cmH₂O)	22	32.45 (14.37)	5	29.8 (23.62)	2.65 (-13.88,19.19)	0.74
PCF (L/min)	26	217.73 (113.76)	6	110 (140.86)	161.73 (51.93 ,271.53)	0.005
SVC%	22	63.86 (17.8)	5	46.2 (33.38)	17.66 (-23.2,58.53)	0.31
ALSFRS-R (x/48)	22	30.36 (5.80)	5	26.4 (12.01)	3.96 (-3.35,11.28)	0.28
		Median (Range)		Median (Range)	Median Diff (CI of Diff)	
Time since Diagnosis to Prescription (Months)	26	10.5 (1,60)	6	14 (2,32)	3.5 (6,14)	0.87*

n=number, SD=standard deviation, 95% CI diff=95% confidence interval of the difference between the two groups, SNIP=Sniff Nasal Inspiratory Pressure, cmH₂O=centimetres of water, PCF=Peak Cough Flow, L/min=Litres per minute, SVC%=Slow Vital Capacity percent predicted, %=percent, ALSFRS-R=Amyotrophic Lateral Sclerosis Functional Rating Scale Revised, Median Diff=difference of median, *=Mann Whitney U Test

5.9.6 Comparison of Characteristics of Participants Prescribed M-IE and LVR and Participants not Prescribed M-IE and LVR

Comparison of demographics of participants prescribed and not prescribed a device are described in Table 5.16 and Table 5.17. There were no significant differences in age and time from diagnosis to study entry ($p > 0.05$). A Chi-square test for independence (with Yates Continuity Correction) (Pallant, 2013) indicated no significant association between site of onset and the prescription of a device, $\chi^2 (1, n=90) = 0.0$, $p=1.0$, $\phi=0.02$.

Table 5.16: Comparison of Demographics of Participants Prescribed and Not Prescribed a Device

	Device		No Device			
	n	Age (Mean (SD))	n	Age (Mean (SD))	Diff (95% CI diff)	p-value
Male and Female	30	63.0 (10.19)	60	60.2 (12.84)	2.8 (-2.55,8.15)	0.30
Male	20	64.25 (9.34)	38	55.95 (13.06)	8.30 (1.70,14.90)	0.2
Female	10	60.5 (11.84)	22	67.55 (8.6)	-7.05 (-14.59,0.50)	0.07

n=number, SD=standard deviation, 95% CI diff=95% confidence interval of the difference between the two groups; Median Diff=difference of median, *=Mann Whitney U Test

Table 5.17: Comparison of Time from Diagnosis to Study of Participants Prescribed and Not Prescribed a Device

	Device		No Device			
	n	Time From Diagnosis to Study Entry (months) (Median (range))	n	Time From Diagnosis to Study Entry (months) (Median (range))	Median Diff (CI of Diff)	p-value
Male and Female	30	6.5 (0,55)	60	7.5 (0,90)	1.0 (3.5,7.0)	0.8*
Spinal	25	7.0 (0,55)	5	8.0 (0,90)	1.0 (3.5,7.5)	0.6*
Bulbar	49	6.0 (2,24)	11	6.0 (0,35)	0 (1.0,12)	0.61*

n=number, CI of diff=95% confidence interval of the difference between the two groups; Median Diff=difference of median, *=Mann Whitney U Test

The average values of SNIP, SVC percent predicted, PCF and ALSFRS-R for participants prescribed a device compared to participants not prescribed a device were calculated using the multilevel repeated measures model for unbalanced follow up (Cnaan et al., 1997) with the site of onset, time between respiratory assessments, time from diagnosis to study entry, age and gender were included as co-variates (Table 5.18). Participants prescribed a device had a statistically significant lower average SNIP, SVC percent predicted, PCF and ALSFRS-R ($p<0.001$) compared to participants not prescribed a device.

Table 5.18: The Average Values of SNIP, SVC percent predicted, PCF and ALSFRS-R for Participants Prescribed a Device Compared to Participants not Prescribed a Device

	Average Score of Participants Prescribed a Device compared to participants not prescribed a Device	Standard Error	p-value
SNIP (cmH₂O)	-18.96	5.20	<0.001
PCF (L/min)	-78.59	1.54	<0.001
SVC percent predicted (%)	-19.11	0.30	<0.001
ALSFRS-R (x/48)	-5.55	0.08	<0.001

SNIP=Sniff Nasal Inspiratory Pressure, cmH₂O=centimetres of water, PCF=Peak Cough Flow, L/min=Litres per minute, SVC%=Slow Vital Capacity percent predicted, %=percent, ALSFRS-R=Amyotrophic Lateral Sclerosis Functional Rating Scale Revised

Participants prescribed M-IE had a statistically significant lower average SNIP, SVC percent predicted, PCF and ALSFRS-R ($p<0.001$) (Table 5.19) compared to participants not prescribed a device.

Table 5.19: The Average Values of SNIP, SVC percent predicted, PCF and ALSFRS-R for Participants Prescribed M-IE Compared to Participants not Prescribed a Device

	Average Score of Participants Prescribed M-IE compared to participants not prescribed M-IE	Standard Error	p-value
SNIP (cmH₂O)	-24.62	6.9764	<0.001
PCF (L/min	-124.75	29.6925	<0.001
SVC percent predicted (%)	-25.39	5.8573	<0.001
ALSFRS-R	-7.56	1.79347	<0.001

SNIP=Sniff Nasal Inspiratory Pressure, cmH₂O=centimetres of water,
PCF=Peak Cough Flow, L/min=Litres per minute, SVC%=Slow Vital Capacity
percent predicted, %=percent, ALSFRS-R=Amyotrophic Lateral Sclerosis
Functional Rating Scale Revised

Participants prescribed LVR had a statistically significantly lower average SNIP ($p=0.01$), SVC percent predicted (0.001) and ALSFRS-R ($p=0.01$) but not PCF ($p=0.07$) (Table 5.20) compared to participants not prescribed a device.

Table 5.20: The Average Values of SNIP, SVC Percent Predicted, PCF and ALSFRS-R for Participants Prescribed LVR Compared to Participants not Prescribed a Device

	Average Score of Participants Prescribed LVR compared to participants not prescribed LVR	Standard Error	p-value
SNIP (cmH₂O)	-15.21	6.0054	0.01
PCF (L/min)	-46.2	25.6214	0.07
SVC percent predicted (%)	-14.99	5.0532	0.001
ALSFRS-R (x/48)	-4.27	1.54040	0.001

SNIP=Sniff Nasal Inspiratory Pressure, cmH₂O=centimetres of water, PCF=Peak Cough Flow, L/min=Litres per minute, SVC%=Slow Vital Capacity percent predicted, %=percent, ALSFRS-R=Amyotrophic Lateral Sclerosis Functional Rating Scale Revised

Table 5.21 describes the changes of SNIP, PCF, SVC percent predicted and ALSFRS-R over time between participants prescribed a device and not prescribed a device and how they are affected by; bulbar compared to spinal onset; an increase in age by one year; an increase of one month since time from diagnosis to study entry and male compared to female gender.

Table 5.21: The Changes of SNIP, PCF, SVC Percent Predicted and ALSFRS-R over Time between Participants Prescribed a Device and not Prescribed a Device

	SNIP (cmH₂O) (p-value)	PCF (L/min) (p-value)	SVC Percent Predicted (%) (p-value)	ALSFRS-R (x/48) (p-value)
Bulbar	-3.29 (0.61)	-81.53 (<0.001)	-6.90 (0.20)	-0.99 (0.55)
Age	-0.92 (<0.001)	-5.82 (<0.001)	-0.14 (0.49)	-0.02 (0.68)
Time from Diagnosis to Study Entry	-0.24 (0.08)	-1.01 (0.10)	-0.34 (0.001)	-0.14 (<0.001)
Male	10.30 (0.07)	87.23 (<0.001)	-3.09 (0.51)	1.05 (0.47)

SNIP=Sniff Nasal Inspiratory Pressure, cmH₂O=centimetres of water, PCF=Peak Cough Flow, L/min=Litres per minute, SVC%=Slow Vital Capacity percent predicted, %=percent, ALSFRS-R=Amyotrophic Lateral Sclerosis Functional Rating Scale Revised

5.9.7 Comparison of Chest Infection Frequency and Antibiotic Use of Participants prescribed and not prescribed M-IE and LVR

The self-report method for collecting chest infection frequency and antibiotic use data were used as there was a 100% response rate. Twenty-eight chest infections were reported by participants prescribed a device. Twenty-seven chest infections were reported by participants who were not prescribed a device. There was a non-statistically significant difference in the number of chest infections reported between participants prescribed and participants not prescribed a device ($p=0.17$) (Table 5.22).

Antibiotics were reported to have treated chest infections on 22 occasions for participants prescribed a device. Antibiotics were reported to have treated chest infections on 18 occasions for participants not prescribed a device. There was a non-statistically significant difference in the number of times antibiotics were reported to treat chest infections reported between participants prescribed and participants not prescribed a device ($p=0.25$).

Table 5.22: Comparison of Self-Reported Chest Infection Frequency and Antibiotic Use between a Device and No Device

	Device		No device			
	n=48		n=60			
		Median (range)		Median (range)	Median Diff (CI of Diff)	p-value
Number of Chest Infections Reported		0 (0,4)		0 (0,6)	0 (0,0)	0.17*
Number of Times Antibiotics Used to Treat Chest Infections		0 (0,4)		0 (0,2)	0 (0,0)	0.25*

n=number, *=Mann-Whitney U test

5.10 Conclusion

This chapter has detailed the results of the prospective observational cohort study. Chapter 6 will answers the questions that were identified in the literature review and will explain the results to support these answers.

Chapter 6: Respiratory Measurements, Physical Function and Airway Clearance Device Prescription over One Year in Amyotrophic Lateral Sclerosis: Discussion

6.1 Introduction

This study of 108 Amyotrophic Lateral Sclerosis (ALS) participants demonstrated that Sniff Nasal Inspiratory Pressure (SNIP), Peak Cough Flow (PCF), Slow Vital Capacity (SVC) percent predicted and Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R) declined at a significant rate over the one year study period. In addition, Mechanical Insufflation Exsufflation (M-IE) and Lung Volume Recruitment (LVR) were prescribed to approximately 30% of the cohort of 108 ALS participants with similar numbers of M-IE and LVR devices prescribed. The type of device prescribed was independent of ALS subtype, but the participants that were prescribed M-IE and LVR who all reported subjective respiratory symptoms had poorer respiratory muscle strength, function, cough strength and physical function than participants not prescribed a device. Respiratory muscle strength and function, cough strength and physical function declined at a significant rate for the whole cohort. Unfortunately, individual rates of decline for participants prescribed M-IE and LVR could not be calculated due to an insufficient number of assessments collected per participant. Approximately one third of participants reported a chest infection and the number of chest infections and the antibiotics reported to treat them were not different between participants prescribed and not prescribed a device. Finally, at study conclusion at one year 80.56% of participants were alive.

This is the first study to quantify the rate of decline of SNIP, SVC and PCF in an Irish ALS cohort; to express decline in SNIP as whole values and to express decline in PCF in a large ALS cohort. This is a clinically useful measure. An awareness of the rate of decline may help anticipate future changes and prompt clinical interventions in a timely manner. This study is also the first to describe a cohort of Irish ALS participants who received M-IE and LVR devices and to analyse the prescription of M-IE and LVR among an ALS cohort. This study has described the respiratory muscle strength and function, cough strength, physical function and respiratory symptoms at the

time of M-IE and LVR prescription in an Irish ALS cohort. This study provides a point of reference for future studies and provides a more complete understanding of cough augmentation device prescription. This chapter will discuss these findings in further detail below.

6.2 Description of the study group

The cohort of recruited participants comprised of more males (65.7%) than females (34.3%). This is consistent with the higher rate of ALS among males than females (Alonso et al., 2009). However, the percentage of males was slightly higher than an Irish ALS cohort study of 1282 cases that reported 56.5% male cases (Rooney et al., 2013). The mean age of participants at diagnosis was 60.16 years, and the mean age at onset was 59.0 years. This is comparable with the mean age at diagnosis of 64.6 years in an Irish ALS cohort (Rooney et al., 2013) and the mean age of ALS onset reported of 58–63 years in an international cohort (Haverkamp et al., 1995). Females were significantly older than males. The time from diagnosis from study entry had a large range of 90 months. This study did not specify a time from diagnosis in the inclusion criteria to allow this study to capture a variety of ALS clinical presentations and all aspects of an ALS cohort. The gender and age of this study cohort was comparable to other reported demographics of Irish and international ALS population based studies, which indicates that this was a representative sample.

6.3 ALS Characteristics

The cohort consisted of a higher proportion of spinal (78.7%) compared to bulbar onset ALS participants. Symptoms commenced marginally more frequently in the upper limbs (48.2%) than the lower limbs (43.5%) in the spinal onset ALS participants. The rate of 78.7% spinal onset ALS participants is also higher than the 58.4% reported in an Irish ALS cohort (Rooney et al., 2013). Consecutive participants were approached for this study and a specified number of spinal and bulbar participants to be recruited were not detailed.

6.4 Baseline Measurements

The baseline measurements of SNIP, PCF, SVC percent predicted and ALSFRS-R varied greatly. SNIP ranged from 5–122cmH₂O, SVC percent

predicted ranged from 20–124%, ALSFRS-R ranged from 8–47 units and PCF had a SD of 153.27L/min. This represents a significant amount of heterogeneity in participants recruited which is likely due to the corresponding large range in time from diagnosis to study entry of 0–90 months. The inclusion criterion did not specify a time from diagnosis, respiratory muscle strength and function or physical function. This was endeavoured to capture a wide variety of participants.

Median SNIP was 45cmH₂O at study entry. This measure indicates the low level of respiratory muscle strength of the participants at study entry. Morgan et al., (2005) demonstrated that a SNIP less than or equal to 40cmH₂O was associated with death within six months. Based upon SNIP scores, 46 participants at study entry were below this level of 40cmH₂O, indicating significant respiratory weakness.

Half of participants had an SVC percent predicted of greater than or equal to 81%, indicating a good overall respiratory function. Only 20 participants had an SVC percent predicted less than 50%. A Vital Capacity (VC) of less than 50% predicted was a predictor of death after six months (Morgan et al., 2005). There is a lack of comparison between SVC percent predicted and SNIP. SNIP measurements identified 46 participants at risk of death within six months. SVC percent predicted may have overestimated respiratory muscle function in the participants and SNIP may have underestimated respiratory muscle strength. This is supported by the research that VC is not sensitive in detecting mild to moderate respiratory weakness and it may have overestimated respiratory muscle function of the participants in this study (Fitting et al., 1999, Polkey et al., 1998). There is research that also suggests that SNIP has a low sensitivity in severe bulbar dysfunction participants (Lyall et al., 2001).

The mean PCF was 346.44L/min. This was above the cough critical threshold of 160 L/min and the 270 L/min associated with respiratory complications (Bach and Saporito, 1996). A number of participants (n=16) had a PCF less than the cough critical threshold of 160L/min and theoretically could not expectorate secretions independently at study entry and possibly had a lower median survival than participants with a PCF

greater than 160L/min. Emerging research has identified the possibility of using PCF as a predictive measure in ALS. This pilot Randomised Control Trial (RCT) investigated the effects of M-IE and LVR in ALS participants and found that a PCF greater than 160L/min had a better median survival of 260 days versus 110 days in participants with PCF less than 160L/min (Rafiq et al., 2015). The majority of the participants in the cohort were in the favourable category of greater than 160 L/min.

PCF was the only baseline measurement to be statistically significantly higher in males than females ($p < 0.0001$) and in spinal than bulbar onset ALS ($p = 0.01$). Bulbar onset ALS participants have reduced laryngeal co-ordination and vocal cord adduction necessary during the compressive phase of cough (Finder, 2010). These are necessary for the compressive phase of cough in order to increase the intrathoracic pressure to generate a strong cough (McCool, 2006). This lower PCF observed in bulbar compared to spinal onset ALS participants could have been as a result of this laryngeal and vocal cord involvement.

The median ALSFRS-R score at study entry was 36 out of a maximum total of 48. ALSFRS-R decreases rapidly in ALS and can predict survival (Kaufmann et al., 2005, Gordon et al., 2004, Cedarbaum et al., 1999, Traynor et al., 2004, Rooney et al., 2016). Participants who had a baseline ALSFRS-R score of less than the median of 38 were 4.4 times more likely to die or require a tracheostomy within a one year study ($p < 0.001$) (Kaufmann et al., 2005). Participants with a score above 38 at baseline had a mean survival of 25.2 months compared to a mean survival of 14.6 months with a score below 38. This study did not describe the ALSFRS-R scores at diagnosis but at study entry and cannot be directly compared to these results; however 62% of participants were below this threshold of 38, indicating poorer survival.

The inclusion criterion in this study did not seek participants at a certain level of respiratory muscle strength and function or physical function. By including participants at different levels of respiratory muscle strength and function and physical function as represented in the baseline measurements allowed us to

explore the realistic scenario experienced by clinicians and their decision making process.

Baseline measurements indicated that this study cohort presented with a wide range of measurements in SNIP, SVC percent predicted, PCF and ALSFRS-R. Two measures SNIP and ALSFRS-R indicated that almost half of participants had a short prognosis.

6.4.1 Respiratory Muscle Strength and Function, Cough Strength and Physical Function

Sniff Nasal Inspiratory Pressure, PCF, SVC percent predicted and ALSFRS-R all declined significantly over the one year study period. The findings confirm observations of previous investigators that ALS declines at a progressive rate (Fitting et al., 1999, Gordon et al., 2010, Rafiq et al., 2015) but also includes several new findings that provide a more complete understanding of the rate of decline of respiratory muscle strength and function, cough strength and physical function in ALS that will be discussed below.

A significant rate of decline in SNIP of 18.72cmH₂O or 37.1% change per year for all the participants in our study was calculated. This is the first study to quantify the rate of decline of SNIP in an Irish ALS cohort and the first to express decline in SNIP as whole values. It is probable that this is a good representation of the rate of decline in SNIP in an ALS cohort, supported by the range in baseline SNIP values of 5–122cmH₂O and a large sample size of 108 participants.

Previous published evidence by Fitting et al, (1999), reported a rate of decline of 50.4% per year of SNIP normal predicted values in the ten of 16 participants that demonstrated a significant negative slope. Direct comparison of the results with this study is difficult for a number of reasons. Firstly, the whole cohort rate of decline was not published. Secondly, SNIP values were expressed as normal predicted values. SNIP values in this study were expressed as whole values to comply with ENCALS standard operating procedure (Appendix 1) and for consistency with other ALS research that did not express SNIP as normal predicted values (Morgan et al., 2005, Andersen et al., 2012, Miller et al., 2009b, Capozzo et al., 2015, Carratu et al., 2011,

Colville et al., 2007, Heritier et al., 1994, Lofaso et al., 2006, Maillard et al., 1998). Thirdly, the mean baseline measurements of SNIP were $65 \pm 18 \text{ cmH}_2\text{O}$ compared to the median of $45 \text{ cmH}_2\text{O}$ found in the present study. Finally, the population size described in the study by Fitting et al (1999) was modest with a total of 10 of 16 participants included for analysis.

In this study, a rate of PCF decline of participants with a range of respiratory muscle weakness and function among a large ALS cohort of 108 participants was investigated. PCF declined at a statistically significant rate of 124.84 L/min or 38.41% change per year. This is the first study to quantify the rate of decline of PCF in an Irish ALS cohort and the first to express decline in PCF in a large ALS cohort.

Peak Cough Flow rate of decline has been reported in a small ALS cohort of 40 weak ALS participants (Rafiq et al., 2015). However, higher and lower rates of PCF decline were reported in this RCT (Rafiq et al., 2015). The PCF rate of decline was 69.24 L/min per year in the M-IE group. PCF did not decline in the LVR group but improved by 10.8 L/min per year. The difference in rates of decline between the two groups was not significant and PCF rate of decline for the whole cohort were not published. The rate of decline in a weaker group might be lower such as in the M-IE group. Participants in the M-IE group had a baseline median PCF of 120 L/min in comparison to the LVR group with a median baseline PCF of 215 L/min . This is in contrast to the higher baseline PCF of a mean 346.44 L/min or a median of 350 L/min . Additionally, a smaller sample size of 20 participants may produce less accurate rates of PCF decline.

The rate of PCF decline of 124.84 L/min or 38.41% change per year calculated provides clinicians with a clinically useful measure that can be used to predict their patient's potential rate of PCF decline and assist their clinical practices. A PCF of less than 160 L/min is associated with an inability to effectively clear secretions and a PCF of less than 270 L/min is associated with respiratory complications (Bach and Saporito, 1996). A PCF close to these thresholds should alert clinicians to the possible implications of respiratory complications that a further decline in PCF may hold and alert clinicians to possible use of the recommended airway clearance devices

such as M-IE and LVR (NICE, 2016, Bott et al., 2009, O'Callaghan et al., 2014, Miller et al., 2009a).

In this study, SVC percent predicted declined at a statistically significant rate of 17.49% predicted or 23.51% change per year. This confirms the progressive nature and decline of respiratory function in ALS observed by previous investigators (Fitting et al., 1999, Baumann et al., 2010). This value is likely to be accurate as it was determined by the large sample size of 108 participants, and the mixed range of ALS participants with an SVC range of 20-124% predicted at baseline within our study population.

However, higher and lower rates of VC decline have been reported by other investigators. Their values range from 5.4% (Rafiq et al., 2015), 24% (Traynor et al., 2004) , 37.2% (Baumann et al., 2010), 42% (Schiffman and Belsh, 1993) and 49% predicated per year (Fitting et al., 1999). Calculating rate of VC decline from various respiratory muscle function levels and different size populations will produce different rates of decline. The rate of decline in a weaker population might be lower such as in Rafiq et al., (2015). Participants with a low respiratory function with a baseline VC percent predicted value of 53.4% were included in this study. In comparison to Fitting et al., (1999), at study entry all participants had a normal baseline muscle function as determined by VC percent predicted of 107%. Additionally, the different smaller sample sizes may produce less accurate rates of VC decline. The above studies had different sample sizes of 16 (Fitting et al., 1999), 24 (Schiffman and Belsh, 1993), 40 (Rafiq et al., 2015), 80 (Baumann et al., 2010) and 97 participants (Traynor et al., 2004).

Amyotrophic Lateral Sclerosis Functional Rating Scale Revised declined at a significant rate of 9.62 units per year or 29.64% change. By analysing function in this Irish ALS cohort over one year a rate of decline of ALSFRS-R has been established. This analysis, which incorporates and confirms the separate observations of previous investigators that ALSFRS-R declines significantly in ALS (Rooney et al., 2016, Gordon et al., 2010).

However, higher and lower rates of ALSFRS-R decline have been reported by Gordon et al., (2010). Their values range from between 6.84 units per year in the first 17 months and 9.76 units per year in the first 18 months

(Gordon et al., 2010). The higher value of 9.76 units per year in the first 18 months is comparable to the finding of 9.62 units per year. The analysis confirms the rate of decline of ALSFRS-R.

The rate of ALSFRS-R decline reported here is indicative of the rapid rate of functional change of ALS patients. Similar to the clinically important use of PCF rate of decline, an awareness of ALSFRS-R rate of decline can facilitate clinicians in their practices. A rapid change in ALSFRS-R score can prompt clinical interventions. However, an awareness of the rate of decline may also help anticipate future changes in physical function and prompt clinical interventions in a timely manner.

By creating plots of SNIP, PCF, SVC percent predicted and ALSFRS-R for the 108 participants over the one year study period starting at study entry, the decline of these values in this Irish ALS cohort has been illustrated. This illustration includes several observations that provide a complete understanding of the decline of SNIP, PCF, SVC percent predicted and ALSFRS-R.

In this study, a number of participants showed an increase followed by a decrease in their scores for SNIP, PCF and SVC percent predicted. Possible explanations of why all participants did not follow the expected linear decline are suggested.

Firstly, a learning effect could be associated with this trend in the assessment of SNIP (Bauer et al., 2012, Uldry and Fitting, 1995, Lofaso et al., 2006). Lofaso et al., (2006), recommended performing a minimum of 10 assessments or an additional 10 assessments if the value was below normal in the first 10 assessments or if it used to assess respiratory decline over time. However, efforts were made to limit this learning effect in this study. The SNIP procedure was performed in accordance of the European Network for the Cure of ALS (ENCALS) standard operating procedure (Appendix 1) and a minimum of 10 times and further assessments were completed if the score was below normal.

Secondly, a learning effect could also be associated with PCF. The psychometric properties of PCF have not been investigated to the same

degree as SNIP, VC and ALSFRS-R in ALS or other cohorts and a learning effect has not been reported in prior studies. The majority of studies that have included PCF assessments in ALS have investigated the immediate effects of interventions on PCF (Senent et al., 2011, Cleary et al., 2013, Sancho et al., 2004) in ALS only and information on the rate of decline over long durations is limited.

Thirdly, a participant's inability to perform repeatable SVC measurements could have influenced the SVC percent predicted plots. The criteria for completing an SVC measurement was 1) the two highest readings had a variability of less than 250 millilitre (ml) or the two highest readings had a variability of less than 10% if the SVC was less than 100ml 2) participants became fatigued and they could not perform further assessments (Miller et al., 2005). A number of participants did not achieve the a variability of less than 250 millilitre (ml) or the two highest readings had a variability of less than 10% if the SVC was less than 100ml before they became fatigued. This possibly contributed to inaccuracies and prevented a linear decline in SVC percent predicted for all participants.

In summary, the significant rate of decline of SNIP, PCF, SVC percent predicted and ALSFRS-R confirms the progressive nature and respiratory and functional decline of ALS (Fitting et al., 1999, Rafiq et al., 2015, Gordon et al., 2010). The rates of decline in SNIP, SVC and PCF are the first reported in a large Irish ALS cohort. Clinical applications of this new information add to the importance of these findings. An awareness of the rate of decline in PCF may have positive clinical implications for clinicians working with ALS patients.

6.5 Mortality

A high percentage of participants (80.56%) were alive at study conclusion. Survival analysis was not appropriate due to the short study period of one year.

6.6 Chest Infection Frequency and Antibiotic Use

Almost one third of participants self-reported a chest infection during this study period. Not all participants received antibiotics to treat a chest infection. Only 40 of the 56 self-reported chest infections were treated with

antibiotics. In comparison to General Practitioner (GP) reports, 47 chest infections among 57 participants were detailed. This indicated a lower chest infection rate of 25.93%. The GPs reported that 41 antibiotics were prescribed for these forty seven chest infections. A higher rate of antibiotic use of 87.23% was reported by GPs to treat these chest infections.

By using self-report measures to capture chest infection frequency and antibiotic use, a picture of the respiratory morbidity among ALS participants has been created. These findings incorporate and support the separate observation of chest infection frequency by Rafiq et al., (2015). Results are similar to the chest infection frequency observed in this study. In this study one third of participants self-reported a chest infection with the use of a diary. A total of 32 chest infections among 40 participants were captured requiring 185 days of antibiotic treatment (Rafiq et al., 2015). The findings also include a new observation on the number of antibiotics used to treat chest infections.

The importance of measuring chest infection frequency is crucial to any study that is assessing the impact of an intervention among ALS participants. Respiratory morbidity is the leading cause of death in this population (Turner et al., 2003). Chest infections further impact an already declining respiratory system. Cough strength and cough effectiveness are further decreased by chest infections in Neuromuscular Disease (NMD) participants (Bach and Saporito, 1996). An existing weak cough may not pose difficulties until a chest infection further decreases cough strength. A cough strength close to the cough critical threshold of 160 L/min (Bach and Saporito, 1996) will be further reduced to below 160 L/min leading to an ineffective cough in the event of a chest infection. Pulmonary morbidity in the form of chest infection frequency and antibiotic use is important to capture these clinically relevant measures.

Contrary to efforts made to collect accurate chest infection frequency and antibiotic use, conflicting reports between participants and GPs existed. These findings highlighted the obstacles that arise in collecting data such as chest infection frequency and antibiotic use for participants. Inaccuracies exist in self-report measures (Bollen et al., 2014, Yuen et al., 2013) (Chapter 9). Chest infection was not defined and this lack of definition could have

underestimated or over estimated the number of chest infections experienced by participants. At each visit the lead researcher asked the participant if they had experienced a chest infection since their last review. Interpretation of a chest infection among participants may have varied. Not all chest infections were treated with an antibiotic. A chest infection that was not medically assessed or treated with antibiotics may not have been reported by participants. Contradictory reports of antibiotic use can be further explained if antibiotics were only necessary for severe chest infections and not for minor infections. Independent of the inaccuracies associated with self-reported measures, 19.44% of participants died during the one year study. The leading cause of death in ALS is respiratory complications (Turner et al., 2003) and chest infections leading up to a participant's deaths could not be captured by the self-reported measure. As a result, the self-report frequency of chest infections could be underestimated. There was a similar limitation in the RCT by Rafiq et al., (2015). A high mortality rate of 52.5% was reported among the participants and chest infections leading up to a participant's death could not have been captured by the self-reported measure of a diary. In this study, chest infection frequency may not have been accurate as a result of the limitations associated with self-report methods, mortality and lack of chest infection definition. Furthermore, information from GPs evidently lacks reliability and consistency with a total response rate of only 52.8% among GPs.

6.7 Prescription

6.7.1 Frequency of M-IE and LVR prescription

The frequency of M-IE and LVR prescription during the one year study was 29.63%. The frequency of M-IE and LVR prescription in an ALS cohort has now been calculated. This evaluation of M-IE and LVR prescription adds to separate findings of the frequency of M-IE prescription among spinal cord injury participants (Crew et al., 2010) but provides a more complete understanding of cough augmentation device prescription.

Data on the frequency of M-IE prescription of 4.6% (41/883) in spinal cord injury participants has been reported (Crew et al., 2010). In this study the complete frequency of M-IE and LVR prescription among a large cohort of

108 participants was reported. In this study, the frequency of M-IE prescription was 12.96%. This frequency is likely to be accurate, as the prescription of M-IE was determined by a direct link with the prescribing physiotherapist at the ALS/Motor Neuron Disease (MND) Multidisciplinary Team (MDT) clinic. However, lower rates of prescription have been observed (Crew et al., 2010). But deducing values of M-IE prescription from retrospective measures is less accurate than the methods undertaken in this study. The frequency of M-IE prescription among this spinal cord injury cohort may have been underestimated as a result of the retrospective design of this study.

The clinical differences of spinal cord injury participants and ALS participants must be highlighted. Spinal cord injury participants who can have respiratory weakness, have a condition which is not progressive in nature (Zimmer et al., 2007). In contrast, ALS is a progressive disease with a median survival of three to five years after symptom onset as a result of respiratory complications (Turner et al., 2003, Andersen et al., 2012). The clinical differences may also explain the lower frequency of M-IE prescription in the spinal cord injury cohort compared to the ALS participants in our study.

The frequency of M-IE and LVR prescription has not previously been explored in ALS participants and the findings of this study are the first to describe a cohort of Irish ALS participants who received M-IE and LVR devices. This study provides a point of reference for future studies. It examines clinical practices of one Irish ALS/MND MDT clinic only. The study participants all attended the same Irish tertiary ALS/MND MDT clinic, and therefore clinical management may not be transferable to other clinical settings as practice may vary.

6.7.2 Characteristics of participants at the time of M-IE and LVR prescription

The findings show that the average time from diagnosis to receiving a device was less than one year. Respiratory muscles strength and function was low with a mean SNIP of 31.96cmH₂O and an SVC percent predicted of 60.59%. Mean cough strength of 241.41L/min was below the cough threshold that is associated with respiratory complications of 270L/min (Bach and Saporito,

1996). Finally, physical function was impaired with a mean ALSFRS-R score of 29.63. All participants had subjective respiratory symptoms. Analysis of demographics revealed that there was no significant difference in age and time from diagnosis to receiving a device between males and females. Time from diagnosis to receiving a device between spinal and bulbar onset ALS participants was not statistically different.

A VC of 1.7L in spinal cord injury participants at the time of M-IE prescription was reported (Crew et al., 2010). In this study, a comprehensive respiratory muscles strength, function, cough strength and physical function assessment at the time of M-IE and LVR prescription among an Irish ALS cohort was reported.

In this study, cough strength was low and respiratory symptoms were present at the time of M-IE and LVR prescription. These results are consistent with published recommendations on the prescription of airway clearance devices in NMD and ALS participants (Bott et al., 2009, Miller et al., 2009a, O'Callaghan et al., 2014, NICE, 2016). The British Thoracic Society/ Association for Chartered Physiotherapists in Respiratory Care (BTS/ACPRC) guidelines recommend that airway clearance strategies are introduced when PCF is equal to or less than 270L/min and that additional secretion management strategies are introduced when PCF is equal to or less than 160L/min in NMD participants (Bott et al., 2009). In ALS specifically, airway clearance devices are recommended when PCF falls below 270L/min (Miller et al., 2009a) All participants prescribed a device had a mean PCF of 241.41L/min. Based on the average PCF for participants they are receiving an airway clearance device later than is recommended.

Irish Guidelines for the Physiotherapy Management of MND recommend the use of M-IE when secretions are causing uncomfortable symptoms and there is an increase in the number of chest infections (O'Callaghan et al., 2014). Subjective respiratory symptoms were reported by all participants with “an ineffective cough” as the most commonly reported symptom.

Physiotherapists recorded subjective respiratory symptoms from a list of seven symptoms at the time of M-IE and LVR prescription. A direct question related to discomfort from secretions was not included in this list, but may be

inferred from the subjective symptom “inability to clear secretions”. An “inability to clear secretions” was reported by 74.2% of participants at the time of M-IE and LVR prescription.

Two participants were prescribed both M-IE and LVR during this study period. LVR was prescribed initially followed by M-IE. Numbers are too small to formulate definite conclusions from this pattern but this pattern also adheres with recommended guidelines (Bott et al., 2009, Miller et al., 2009b, NICE, 2016).

This is the first study to analyse the prescription of M-IE and LVR among an ALS cohort. This study has described the respiratory muscle strength and function, cough strength, physical function and respiratory symptoms at the time of M-IE and LVR prescription in an Irish ALS cohort. Similar to other findings in this study, the clinical practices of one Irish ALS/MND MDT clinic only were included, and therefore clinical management may not be transferable to other clinical settings as practice may vary.

6.7.2.1 Differences between Participants Prescribed M-IE and LVR at the time of M-IE and LVR prescription

Participants prescribed M-IE had a significantly lower SNIP ($p=0.05$) and PCF ($p=0.001$) and non-statistically significant lower SVC percent predicted ($p=0.21$), ALSFRS-R ($p=0.36$) and time from diagnosis ($p=0.52$), compared to participants prescribed LVR.

As discussed above, participants prescribed a device had a mean PCF of 241.41L/min. Based on the average PCF for participants; they are receiving an airway clearance device later than is recommended (Bott et al., 2009, Miller et al., 2009a). However, when the results were stratified into M-IE and LVR devices, the mean PCF was 159.64L/min and 305L/min respectively. The physiotherapists within this ALS/MND MDT clinic prescribed M-IE to the weaker participants confirmed by a lower SNIP and SVC percent predicted values of 25.35cmH₂O and 54.58% respectively. This is consistent with the NICE MND Guidelines recommendation of introducing M-IE if LVR is not effective or during a chest infection (NICE, 2016). The physiotherapists possibly considered that LVR was ineffective for these participants and

prescribed M-IE. This study did not investigate the physiotherapist's further clinical reasoning practices and the assumption can only be inferred.

A surprising finding was that, although there was a statistically significant difference in two respiratory measurements in SNIP and PCF, there was a non-statistically significant difference in SVC percent predicted in the participants prescribed M-IE and LVR. VC has a poor sensitivity in detecting mild to moderate respiratory weakness (Fitting et al., 1999, Polkey et al., 1998). This limitation could possibly explain why SVC percent predicted was not statistically significant. SVC may not have been as sensitive as SNIP and PCF in detecting differences between participants.

6.7.3 Differences between Spinal and Bulbar ALS Participants at the Time of M-IE and LVR Prescription

Site of onset did not influence the type of device prescribed. Spinal participants received nine M-IE and 16 LVR devices. Spinal onset ALS participants had a statistically significantly higher PCF ($p=0.005$), a non-statistically significantly higher SNIP ($p=0.74$), SVC percent predicted ($p=0.31$), ALSFRS-R ($p=0.28$) and shorter time from diagnosis ($p=0.87$), compared to bulbar onset ALS participants.

An interesting finding was that the only statistically significant measurement was PCF. PCF was higher among spinal compared to bulbar onset ALS participants. The significant difference could be attributed to the possible involvement of reduced laryngeal co-ordination in bulbar onset ALS participants. This prevents glottic closure and vocal cord adduction necessary for the compressive phase of cough. Cough strength is reduced as a result of lower interthoracic pressures and limited isometric contraction of the expiratory muscles (Finder, 2010).

Site of onset was independent of device prescribed in this study. This is a surprising finding for two reasons. Firstly, the outcomes of Non-Invasive Ventilation (NIV) use in bulbar onset ALS participants have had different outcomes to spinal onset ALS participants. NIV has been shown to increase survival and Quality of Life (QOL) in an ALS RCT (Bourke et al., 2006). Mean survival was 48 days longer in the NIV group compared with the standard care group. However, the NIV did not improve survival of patients with

severe bulbar involvement. Improvements in QOL were observed and NIV is recommended for the use in severe bulbar involvement patients for this purpose. Secondly, Rafiq et al., (2015) suggested that M-IE could possibly have a negative impact in severe bulbar dysfunction participants. The authors discussed the possibility of the positive insufflation pressure of M-IE blowing excess saliva from the upper airways into the respiratory tract, placing the participant at an increased risk of chest infections. The authors recommended that M-IE should be used cautiously in this subgroup however; this study was not powered for subgroup analysis and could not make a definite conclusion. Other studies stratified results into bulbar and spinal participants (Mustfa et al., 2003, Sancho et al., 2004, Senent et al., 2011). No definite trend could be identified with conflicting findings among the studies. Bulbar involvement did not influence device prescription in this study despite known poorer outcomes in NIV use of severe bulbar dysfunction. However, the results were not stratified into level of bulbar dysfunction to make a definite conclusion.

6.7.4 Comparison of Characteristics of Participants Prescribed M-IE and LVR and Participants not Prescribed M-IE and LVR

This study identified a number of differences in the characteristics of the participants prescribed M-IE and LVR compared to participants not prescribed M-IE and LVR. The results demonstrate that participants prescribed a device had a statistically significantly average lower SNIP of 18.96cmH₂O, PCF of 78.59L/min, SVC percent predicted of 19.11% and ALSFRS-R of 5.55 units compared to participants not prescribed a device.

Stratification of results into M-IE and LVR revealed differences between participants prescribed M-IE and LVR. The participants prescribed M-IE had lower SNIP, PCF, SVC percent predicted and ALSFRS-R measurements than participants prescribed LVR when compared to the whole cohort.

Participants prescribed M-IE had a statistically significantly average lower SNIP of 24.62cmH₂O, PCF of 124.75L/min, SVC percent predicted of 25.39% and ALSFRS-R of 7.56 units compared to participants not prescribed a device. Additionally, participants who were prescribed LVR had a statistically significantly ($p<0.001$) average lower SNIP of 15.21cmH₂O, SVC percent predicted of 14.99% and ALSFRS-R of 4.27 units and a non-

significantly lower PCF of 46.2L/min compared to participants not prescribed a device. Time from diagnosis to study entry and site of onset were not different for participants that were prescribed and not prescribed a device.

Site of onset, age, time from diagnosis to study entry and gender influenced changes of SNIP, PCF, SVC percent predicted and ALSFRS-R in participants who were prescribed a device. In those who received a device: bulbar onset was associated with a lower PCF of 81.53L/min ($p<0.001$) compared to spinal onset ALS; an increase in age by one year was associated with a decrease of SNIP of 0.92cmH₂O ($p<0.001$) and PCF of 5.82L/min ($p<0.001$); each month in time from diagnosis to study entry was associated with a decrease of SVC percent predicted of 0.34% ($p=0.001$) and ALSFRS-R of 0.14 ($p<0.001$) units; male participants had a slower decline in PCF of 87.23L/min ($p<0.001$) compared to females. Not all measurements were statistically significant.

The respiratory weakness of participants prescribed M-IE and LVR by using a multilevel repeated measures model for unbalanced follow up (Cnaan et al., 1997) for one year of longitudinal measurements of SNIP, SVC percent predicted, PCF and ALSFRS-R was detailed. This analysis which incorporates and confirms the separate observations of previous investigators who included weaker ALS participants in M-IE and LVR ALS studies (Senent et al., 2011, Rafiq et al., 2015, Cleary et al., 2013), includes several new observations that provide a more complete understanding of this level of respiratory involvement. Studies had different inclusion criteria but all reflected signs of respiratory weakness, including the use of NIV for two months (Senent et al., 2011), evidence of respiratory failure as defined by criteria requiring NIV (Rafiq et al., 2015) or use of LVR prior to study commencement (Cleary et al., 2013). Only one study specified a PCF measurement of less than 270 L/min (Senent et al., 2011). This lower respiratory muscle weakness and function and physical function has now been quantified in the form of SNIP, PCF, SVC percent predicted and ALSFRS-R for both M-IE and LVR in an ALS cohort by the findings.

6.7.5 Comparison of Chest Infection Frequency and Antibiotic Use of Participants Prescribed and Not Prescribed M-IE and LVR

Contrary to the hypothesis, there was no statistically significant difference in the number of chest infections ($p=0.17$) and antibiotics used to treat them ($p=0.25$) in participants prescribed M-IE and LVR to participants who were not prescribed M-IE and LVR. Twenty-eight chest infections were reported by participants prescribed a device and 27 chest infections were reported by participants who were not prescribed a device. Antibiotics were used 22 times in participants prescribed a device and 18 times in participants not prescribed a device.

It was surprising that there was no statistically significant difference in the number of chest infections reported between participants prescribed a device and not prescribed a device. Participants who were prescribed M-IE and LVR had average lower respiratory measurements when compared to participants who were not prescribed a device. A chest infection is more likely in a participant with lower respiratory measurements, however, this was not observed. The use of M-IE and LVR may have prevented chest infections in these weaker participants. However, an RCT was not undertaken and the findings cannot be confirmed.

6.8 Limitations

The discussion has mentioned some of the limitations encountered while undertaking this research study. The following section will provide more details of these limitations.

The demographics of the participants included have provided a broad spectrum of the ALS cohort. Restrictions of respiratory muscle strength and function, cough strength or time from diagnosis were not implemented in the inclusion criterion to allow a broad range of participants to be recruited. This has resulted in a large range of baseline measurements at study entry and it has also limited follow up of a small portion of participants that died soon after recruitment. This broad range of baseline measurements also posed statistical challenges. A number of assessments were not normally distributed and limited the number of parametric tests that could be performed.

Methodological limitations exist. One limitation is the unequal number of assessments among participants over the one year study. Another limitation of the method is that the time between measurements varied among participants. In total, a large number of assessments were completed, however, the number of measurements among participants ranged from one to six. Scheduled appointments with equal time durations between assessments for this study were not specified. Unfortunately, this scenario is difficult to avoid in a clinical setting. In an effort to reduce burden on the participants and their families, participants were assessed at their routine ALS/MND MDT clinic appointment.

A third limitation of the method is that a proportion of ALS patients were not represented in this study. This research study excluded participants with a diagnosis of frontotemporal dementia. This exclusion criterion has prohibited the analysis of approximately 15% of the ALS cohort (Ringholz et al., 2005). Participants with ALS with frontotemporal dementia were excluded as diagnosed by the consultant neurologist. This decision to exclude participants with frontotemporal dementia can be justified. It was considered that participants with frontotemporal dementia would not be able to perform the required assessments as a result of changes in executive dysfunction (Elamin et al., 2011). In addition, it was questioned if all participants with frontotemporal dementia could provide informed consent. This exclusion criterion has prohibited the analysis of approximately 15% of the ALS cohort.

A fourth limitation to the method was measuring chest infection frequency and antibiotic use. Firstly, although there was a 100% response rate, self-report measures can be inaccurate (Bollen et al., 2014, Yuen et al., 2013). Secondly, there was a low response rate of 52.8% by GPs. Thirdly, a participant's inability to self-report a chest infection following death may have underestimated the number of chest infections among participants. A total of 19.44% of participants had passed away at study conclusion. Death as a result of respiratory complications is the number one cause of death in ALS (Turner et al., 2003). A chest infection is likely to have occurred prior to death but this could not have been reported and collected. Fourthly, a chest infection was not defined to participants. This may have lead to different interpretations of what a participant considered to be a chest infection. It is

possible that GPs may have reported a chest infection that occurred immediately before death but this was not clarified. The most accurate method of quantifying chest infection frequency and antibiotic use is debatable. The methods of self-report and GP report were limited. Alternative methods could include pharmacy records to accurately determine antibiotic prescription. However, this would only account for chest infections that were treated for by a doctor and required antibiotics for treatment.

Statistical limitations were encountered as a result of the above methodological limitations. As a result, the rates of decline could not be stratified into devices or no devices. Thus, the objective to compare the rates of decline of SNIP, SVC percent predicted, PCF, and ALSFRS-R of participants prescribed M-IE and LVR to participants who were not prescribed M-IE and LVR was not achieved and this hypothesis could not be tested.

Data was missing for some participants, posing a further statistical challenge. A total of 27 SNIP, PCF, SVC percent predicted and ALSFRS-R data was missing over the one year study. A multilevel repeated measures model controls for missing data (Cnaan et al., 1997) but a complete data set would have provided more in depth statistical analysis. This data was not gathered as the participants were too unwell, had pain, left for transport or were too fatigued to complete further assessments. Unfortunately, this is a common clinical scenario and one that could not have been avoided.

Caution should be taken when interpreting the results of this one year prospective longitudinal study. This study examined the clinical practices of one Irish ALS/MND MDT clinic only. Clinical management and practices vary among ALS/MND MDT clinics and therefore the results may not be transferrable to other clinical settings.

6.9 Considerations for Future Research

The lack of robust evidence to support or not support the use of M-IE in NMD participants has been identified by a Cochrane review in 2013 (Morrow et al., 2013). It concluded that RCTs were required to determine the safety and effectiveness of M-IE in NMD participants. Since this review in 2013, only one pilot RCT evaluating M-IE and LVR in ALS has been published (Rafiq et

al., 2015). This RCT reported non-statistically significant findings in the number of chest infections, the number of days requiring antibiotics, hospitalisation rates, median survival, QOL, SVC and PCF decline between the M-IE and LVR groups. Limitations to this RCT included a small sample size of 20 participants in each group and a high mortality rate of 69% in the M-IE group. A larger scale RCT similar to this pilot study with the addition of a control group would enhance the available research of M-IE and LVR in ALS. Analysis of SNIP, PCF, SVC percent predicted, ALSFRS-R, QOL, chest infection frequency, number of days requiring antibiotics, hospitalisation rates could commence at diagnosis. Randomisation of participants into one of the three groups when PCF is between 270L/min and 300L/min could occur. Assessment could continue throughout their disease process until death. Results could also be stratified in non-bulbar, mild, moderate and severe bulbar dysfunction participants to evaluate differences between subtypes. This larger longer RCT would make definite conclusions on the efficacy of M-IE and LVR and also add to the shape of decline of SNIP, PCF, SVC percent predicted and ALSFRS-R in ALS participants. However, withholding an airway clearance device from the control group would create an ethical dilemma.

A study to determine the optimum disease stage or clinical measurement to commence airway clearance strategies is required. Airway clearance strategies are recommended when PCF is equal to or less than 270L/min and additional secretion management strategies are introduced when a PCF is less than or equal to 160L/min (Bott et al., 2009, Miller et al., 2009a). The findings of M-IE and LVR prescription were in keeping with these recommendations. Participants were prescribed M-IE and LVR at an average PCF of 159.64L/min and 305L/min respectively. These recommendations are based largely on the work performed by Bach and Saporito, (1996). Successful decannulation occurred only in NMD participants with a PCF greater than 160L/min. This cough critical threshold may not be applicable to the ALS population. An RCT similar to the above recommendations but that comprises of a group that are introduced to M-IE and LVR at an earlier stage when PCF is approximately at 400L/min is suggested. Analysis of rate of

decline of respiratory and physical function measurements would provide information on the optimum time to implement M-IE and LVR devices.

Adherence to M-IE and LVR is paramount to determine their efficacy among ALS participants. Self-reported measures in exercise are limited and are widely described (Bollen et al., 2014, Yuen et al., 2013) and cannot be used to accurately assess adherence. A device to accurately measure adherence would confirm the levels of adherence in such RCT as described above. A device to measure LVR adherence has been developed as part of this thesis and is detailed in Chapter 9. Results could also be stratified into adherent and non-adherent groups, presuming not all participants will be adherent with M-IE or LVR. Frequency of the adherent group could be further stratified to evaluate findings on the frequency of M-IE and LVR use to determine the optimum frequency of M-IE and LVR use in ALS participants.

This study evaluated the first year of data that is planned to continue for a total of three years. This additional two year data will provide more data on M-IE and LVR prescription and further information on the longitudinal decline of SNIP, PCF, SVC percent predicted and ALSFRS-R. To date, a study of this duration evaluating M-IE and LVR study in ALS does not exist.

Evaluating chest infection frequency and antibiotic use among participants evidently had limitations within this study. However, alternative means of monitoring chest infection frequency and antibiotic use to increase accuracy does not exist. This is an important factor to consider in future research when assessing respiratory morbidity.

This chapter has detailed and discussed the findings of the one year prospective longitudinal and observational cohort study. The study limitations and considerations for future research were also described. Chapter 7 will conclude the Respiratory Measurements, Physical Function and Airway Clearance Device over One Year in Amyotrophic Lateral Sclerosis Study.

Chapter 7: Respiratory Measurements, Physical Function and Airway Clearance Device Prescription over One Year in Amyotrophic Lateral Sclerosis: Conclusion

This prospective longitudinal observational cohort study measured respiratory muscle weakness and function, cough strength, physical function, chest infection frequency, antibiotic use and survival over a one year period. This evaluation is the first to report the rate of decline of Sniff Nasal Inspiratory Pressure (SNIP) and Peak Cough Flow (PCF) in an Irish Amyotrophic Lateral Sclerosis (ALS) cohort; to express decline in SNIP as whole values and to express decline in PCF in a large ALS cohort. The significant rate of decline of SNIP, PCF, Slow Vital Capacity (SVC) percent predicted and Amyotrophic Lateral Sclerosis (ALSFRS-R) confirms the progressive nature and respiratory and the physical functional decline of ALS (Fitting et al., 1999, Rafiq et al., 2015, Gordon et al., 2010). The frequency of Mechanical Insufflation Exsufflation (M-IE) and Lung Volume Recruitment (LVR) prescription and the respiratory muscle strength and function, physical function and respiratory symptoms at the time of M-IE and LVR prescription is detailed. To our knowledge, this has not been described in the literature and provides a point of reference for future studies.

Respiratory muscle strength measured by SNIP, respiratory muscle function measured by SVC, cough strength measured by PCF, physical function measured by ALSFRS-R, chest infection frequency and antibiotic use by self-report and General Practitioner (GP) report methods was utilised. In addition, a cross sectional study observed the prescription of M-IE and LVR by assessing SNIP, SVC percent predicted, PCF and ALSFRS-R at the time of M-IE and LVR prescription. In conjunction, the subjective symptoms described by the prescribing physiotherapist were recorded.

The literature firstly identified that M-IE and LVR is safe to use in ALS participants. Secondly, it had positive changes in cough strength but these changes were over short duration studies only. Thirdly, it highlighted the limited evidence of the effect of M-IE and LVR on respiratory morbidity such as chest infection frequency and antibiotic use. Finally, no information on the clinical practices of M-IE and LVR prescription existed. The relevant and

suitable outcome measures were analysed in the development of methodology chapter, justifying the use of SNIP, PCF, SVC and ALSFRS-R. By using a prospective longitudinal observational cohort study over a one year period outlined in the methodology chapter the rates of decline in SNIP, SVC percent predicted, PCF and ALSFRS-R for an Irish ALS cohort were calculated at a rate of 18.72cmH₂O, 17.49%, 124.84L/min, 9.62 units per year respectively. This study also identified the differences in SNIP, SVC percent predicted, PCF and ALSFRS-R measurements of participants prescribed and not prescribed a cough augmentation device.

Site of onset or time from diagnosis were not statistically significantly different, refuting the first hypothesis that there would be a statistically significant difference in disease characteristics of participants prescribed M-IE and LVR compared to participants not prescribed M-IE and LVR. Individual rates of decline for participants prescribed M-IE and LVR could not be calculated due to an insufficient number of assessments collected per participant and consequently the second hypothesis is unanswered. Furthermore, there was no association between M-IE and LVR and chest infection frequency and antibiotic use refuting the final hypothesis that there would be a statistically significant difference in the number of chest infections and antibiotics used to treat them in participants prescribed M-IE and LVR to participants who were not prescribed M-IE and LVR. Finally, 80.56% of participants were alive at study conclusion.

A large scale RCT to formulate definite conclusions on the efficacy of M-IE and LVR in ALS participants is required. Additionally, a study to determine the optimum disease stage or clinical measurement to commence airway clearance strategies is also required.

To assist with a necessary RCT, an accurate method of measuring adherence is necessary such as a sensitive and specific electronic LVR adherence device (Chapter 9).

This research has provided novel comprehensive research into the frequency of M-IE and LVR prescription and the respiratory strength, function, cough strength, physical function and respiratory symptoms at the time of M-IE and LVR prescription in ALS. To our knowledge, this has not

been described in the literature. This provides a point of reference for future studies and will provide a point of reference for physiotherapists to guide their clinical practices.

The study results confirmed the deterioration in respiratory muscle weakness, function and physical function in an ALS cohort and provide novel information regarding the rates of decline. This evaluation is the first to report the rate of decline in SNIP, SVC and PCF in an Irish ALS cohort and the first to report the rate of decline in PCF in a large ALS cohort.

Limitations existed in the form of the methodological challenges of an unequal number of measurements, a low number of measurements performed in a number of participants and unbalanced follow up and a complete analysis of an ALS cohort was not described. Frontotemporal dementia patients were excluded from our study and thus 15% of an ALS cohort was not described.

The correct and accurate methodological approach to measure respiratory morbidity such as chest infection frequency and antibiotic use remains undetermined. This was a limitation in our study reflected in the discrepancies between self-report and GP report measures and the poor response rate of GPs.

Chapter 8: Experience and Usability of Mechanical Insufflation Exsufflation and Lung Volume Recruitment in Amyotrophic Lateral Sclerosis

8.1 Introduction

This chapter will present a study that investigated the participant self-reported experience and usability of Mechanical Insufflation Exsufflation (M-IE) and Lung Volume Recruitment (LVR) in Amyotrophic Lateral Sclerosis (ALS) study. It will firstly review the literature on participant experience and usability of M-IE and LVR. The methods used to assess experience and usability will be described and the results and discussion will be detailed. Finally, study limitations will be explored and recommendations of future research will be suggested.

8.2 M-IE and LVR Patient Experience

There is limited published evidence on the usability and participant self-reported benefits experienced by ALS M-IE and LVR users. Research to date has focused on the physical effects of M-IE and LVR (Rafiq et al., 2015, Cleary et al., 2013, Sancho et al., 2004). Studies have explored self-reported health and lifestyle benefits with the use of M-IE in Neuromuscular Disease (NMD) (Mahede et al., 2015, Moran et al., 2015) and preference between endotracheal suctioning and M-IE in spinal cord injury patients with tracheostomies (Garstang et al., 1999). Senent et al., (2011) investigated the self-reported effectiveness and comfort of seven airway clearance techniques including M-IE and LVR. Quality of Life (QOL) measures with use of M-IE and LVR were measured as part of a larger Randomised Control Trial (RCT) (Rafiq et al., 2015).

Quality of Life did not change with the introduction of M-IE and LVR in ALS and NMD participants (Rafiq et al., 2015, Kaminska et al., 2015). In an RCT comparing M-IE and LVR, there was a non-significant increase in the LVR group (Rafiq et al., 2015). There was a non-statistically significant difference before and after a three-month intervention of LVR in ALS (Kaminska et al., 2015). Although QOL did not improve in ALS, QOL did not decrease with the introduction of M-IE and LVR.

Self-reported comfort and efficacy of M-IE is high in ALS in tracheostomy and self-ventilating participants. M-IE was reported to be more comfortable and effective than suctioning (Sancho et al., 2003). Efficacy and comfort of seven airway clearance devices were rated on a 10-point visual analogue scale. M-IE was rated the most effective and second most comfortable device. LVR was reported to be the second most effective and the third most comfortable device. LVR was reported to be more comfortable than M-IE in bulbar ALS participants (Senent et al., 2011).

Positive and negative lifestyle aspects have been reported in NMD children and adults with home M-IE use. From a quantitative survey, 88% of NMD participants agreed that M-IE had improved their respiratory health, 94% said they would recommend it to other NMD patients and 91% were happy with the use of M-IE in their home (Mahede et al., 2015). Participants reported that the use of M-IE gave them reassurance during a choking episode. This is clinically relevant as choking is more common in ALS than healthy controls (Hadjikoutis et al., 2000). A qualitative research investigated the use of home M-IE in children with NMD. The use of M-IE in the home was positive with parents having a sense of security to manage their child's health and avoid hospital admissions (Moran et al., 2015). Negative comments included the size and weight of the machine and the time required to administer the treatments. M-IE was also considered a disruption to lifestyle and a marker of deterioration of their condition (Moran et al., 2015).

Adherence to M-IE, once prescribed has been investigated and reports range from 47.6% (Bento et al., 2010) to 73% (Mahede et al., 2015) in NMD and ALS participants. Self-reported adherence of 59% was reported in M-IE and 71% in LVR (Rafiq et al., 2015). In this study, severe bulbar dysfunction was associated with non-adherence. In addition, three participants did not feel that they required an airway clearance device. One study reported a daily compliance rate of 47.6% among NMD participants (Bento et al., 2010). The ALS participants in this study had a daily compliance rate of 60%. The daily frequency ranged from one to six times a day. The remaining 40% used M-IE during acute exacerbations only.

All adherence assessments were completed by self-reported measures. A self-administered paper based questionnaire was completed in one study (Mahede et al., 2015) and participants completed a diary in a second (Rafiq et al., 2015). The third study, did not describe the self-report method undertaken (Bento et al., 2010). The methods undertaken to collect adherence rates questions the accuracy of the varying reported adherence rates in the above studies.

Future studies investigating the efficacy of airway clearance devices would benefit from accurate and objective data on adherence. Currently MIE devices can record adherence and frequency of use. However, LVR relies on self-reported adherence methods. This is a challenge in the investigation of the efficacy of this intervention as poor adherence may be a factor in determining the efficacy of LVR use.

The factors that contribute to caregiver burden include level of disability, depression, low mood, anxiety and total distress (Burke et al., 2015). Caregiver burden has been reported to be an outcome of physical deterioration that increases with the progression of ALS (Chio et al., 2005).

Caregiver burden was reported by parents of NMD children (Moran et al., 2015). A frequently disrupted lifestyle was reported by parents of the NMD children using M-IE at home. This more commonly occurred when the parent was the sole operator of the device. This could indicate a lack of M-IE education among other carers. In a second study (Rafiq et al., 2015), there was non-significant difference in carer strain between carers of participants prescribed M-IE and LVR. Carer strain before and after prescription was not assessed. There is a requirement for further investigation to assess the impact of this responsibility on the caregiver to administer such a device.

The published evidence on the usability and participant self-reported benefits experienced by ALS M-IE and LVR users is limited. Previous investigators self-reported comfort and efficacy and QOL, however, areas such as the usability, level of assistance, effect on speech volume and the self-reported effect of M-IE and LVR on cough strength during a chest infection have not been assessed (Senent et al., 2011, Rafiq et al., 2015). It is also important to

consider the level of assistance that may be required for the successful use and adherence of M-IE and LVR in the home setting.

8.3 Research Question

M-IE and LVR usability has not been assessed in ALS participants. Their perception of increase in cough strength and comfort over a longer duration of M-IE and LVR is unknown. Perceived effect on speech volume and the self-reported effect of M-IE and LVR on cough strength during a chest infection are also unclear.

This study had one aim, to evaluate the experiences of participants who were prescribed M-IE and LVR.

The objectives were:

1. To assess M-IE and LVR usability
2. To measure self-reported adherence
3. To evaluate the self-reported effects of M-IE and LVR on cough strength and speech volume
4. To evaluate the self-reported effects of M-IE and LVR on cough strength during a chest infection

8.4 Methodology

8.4.1 Study Design

This was a cross sectional study which took place concurrently with the prospective observational cohort study (Chapter 4). A self-administered 13 item questionnaire was developed and used to collect data. The aim of this study was to evaluate the experiences of participants who were prescribed M-IE and LVR.

8.4.2 Setting

This study took place at a tertiary ALS/Motor Neuron Disease (MND) Multidisciplinary Team (MDT) clinic in Beaumont Hospital Dublin. Participant experience and usability with M-IE and LVR was assessed at the ALS/MND MDT clinic.

8.4.3 Ethical Considerations

Beaumont Hospital Medical Ethics Committee and RCSI Research Ethics Committee granted ethical approval (Appendix 3, 4 and 5).

8.4.4 Sample Size

A sample size to evaluate the experiences of participants who were prescribed M-IE and LVR was not calculated. The prospective observational cohort study had no intervention and the number of participants that would be prescribed a device was unknown.

8.4.5 Participants

8.4.5.1 Recruitment

Participants were recruited from the ALS/MND MDT clinic between August 27th 2015 and March 31st 2016. The inclusion and exclusion criteria described in Chapter 4.7.2 were applied. The participants prescribed M-IE or LVR (Chapter 4.9) were invited to complete the questionnaire.

8.4.5.2 Instrument Development

A questionnaire was developed to assess the experience and usability of M-IE and LVR. The questionnaire was a 13 item self-administered questionnaire (Appendix 11). The questionnaire was developed by the lead researcher and it does not have any historical or comparative data. The questionnaire was piloted for the first three participants.

Ten Likert items with corresponding Likert scales were used. Two questions were multiple choices. One question was a yes/no answer. There was an optional comments section as the final component of the questionnaire.

The Likert scale is an ordered scale. Participants were asked to rate their level of agreement to items that related to their experience with the use of the M-IE or LVR. A five point scale from strongly disagree to strongly agree with numbered options as shown in Table 8.1 was used.

Table 8.1: Likert Scale

Strongly Disagree				Strongly Agree
1	2	3	4	5

The questionnaire commenced with an introduction. This instructed the participant to answer the questions based upon their experience using M-IE and LVR. The prescribed device was first established. Question 2 identified if the participant used the device alone or with a carer or family member. Question three and four aimed to identify participant adherence and frequency of use. Questions five, six, seven, eight, nine, 11, 12 and 13 used Likert statements and corresponding Likert scales. The statement topics comprised of ease, comfort, cough strength, confidence, usability, speech volume and cleaning the device. Questions 10 and 11 sought information on chest infection occurrence since last clinic assessment. If chest infection had occurred information was sought on the ability of the device to assist with cough strength. Finally there was a comments section where participants could provide additional feedback on their experience and usability of M-IE and LVR.

8.4.5.3 Questionnaire Assessment

The questionnaire was completed by participants at the first clinic visit after the prescription of M-IE or LVR (Chapter 4.9). The participant completed it alone or with a family member or carer. It was decided to administer the questionnaire at this time as participants had sufficient time to become familiar with the device.

8.4.6 Statistical Analysis

SPSS was used for analysis. Data was entered into SPSS. Nominal data collected for questions one, two and 10 were presented as frequencies. Likert results were collapsed into agree, neutral or disagree categories and expressed as a percentage. These results were further stratified into site of onset and device prescribed.

8.5 Results

8.5.1 Introduction

The questionnaire aimed to evaluate the experiences of participants who were prescribed M-IE and LVR and addressed four areas. Firstly it assessed M-IE and LVR experience and usability, secondly it measured self-reported adherence, thirdly it evaluated the self-reported effects of M-IE and LVR on cough strength and speech volume and finally it evaluated the self-reported effect of M-IE and LVR on cough strength during a chest infection.

8.5.2 Demographics

A total of 32 M-IE and LVR devices were prescribed to participants. Of these participants, three had passed away and ten had not returned to clinic before the study time frame was completed (28th August 2016). Questionnaires were completed by the remaining 19 (59.38%) participants. The data were stratified to identify differences between spinal and bulbar onset ALS and differences between M-IE and LVR. The completed questionnaires described the experiences of seven (36.8%) participants prescribed M-IE and 12 (63.2%) participants prescribed LVR.

Of the 19 participants, nine (47.4%) were male and 13 (68.4%) had spinal onset ALS (Table 8.2). Mean age at study entry was 65.1 years and this was not significantly different between males and females ($p=0.83$ mean difference = -0.96 years, 95% Confidence Interval (CI) = (-10.58, 8.67)). Questionnaires were returned on average 60 ± 21 days after device prescription and 13.6 ± 9.6 months after diagnosis.

Table 8.2: Demographics of Participants that Completed the Questionnaire

	Mean (SD)
Age (years)	65.1 (9.8)
Male	65.6 (6.2)
Female	64.6 (12.6)
Time Since Prescription of Device to Completion of Questionnaire (Days)	60.4 (20.9)
Time Since Diagnosis to Completion of Questionnaire (Months)	13.6 (9.6)
	Number (%)
Gender	
Male	9 (47.4)
Female	10 (52.6)
Site of Onset	
Spinal	13 (68.4)
Bulbar	6 (31.6)
Device	
M-IE	7 (36.8)
LVR	12 (63.2)

SD=Standard Deviation, M-IE=Mechanical Insufflation Exsufflation, LVR=Lung Volume Recruitment

8.5.3 Level of Dependence

Of the 19 participants, 10 (52.6%) reported that they used M-IE and LVR with support from a family member or carer, seven (36.8%) used their device independently and two (10.5%) used it independently or with support from a family member or carer. A higher percentage of participants (58.3%) required assistance with the use of LVR than M-IE (42.9%). A higher percentage of participants with spinal onset ALS (61.5%) required assistance when compared to bulbar onset ALS (33.3%).

8.5.4 Ease of Use

Thirteen (72.2%) participants agreed and two (11.1%) participants disagreed that the devices were easy to use. Stratification by type of device showed that a similar percentage of participants agreed that both M-IE (71.4%) and LVR (72.7%) were easy to use. No participants who were prescribed M-IE disagreed that it was easy to use however, two participants (18.2%) disagreed that the LVR was easy to use. Stratification by onset of ALS showed that spinal onset was associated with higher percentage of agreement of 84.6% (n=11) compared to 40% (n=2) of bulbar onset ALS. Spinal onset was also associated with a higher level of disagreement as two (15.4%) participants disagreed that the devices were easy to use. Participants with bulbar onset did not disagree that the devices were easy to use but 60% (n=3) gave a neutral response (Figure 8.1).

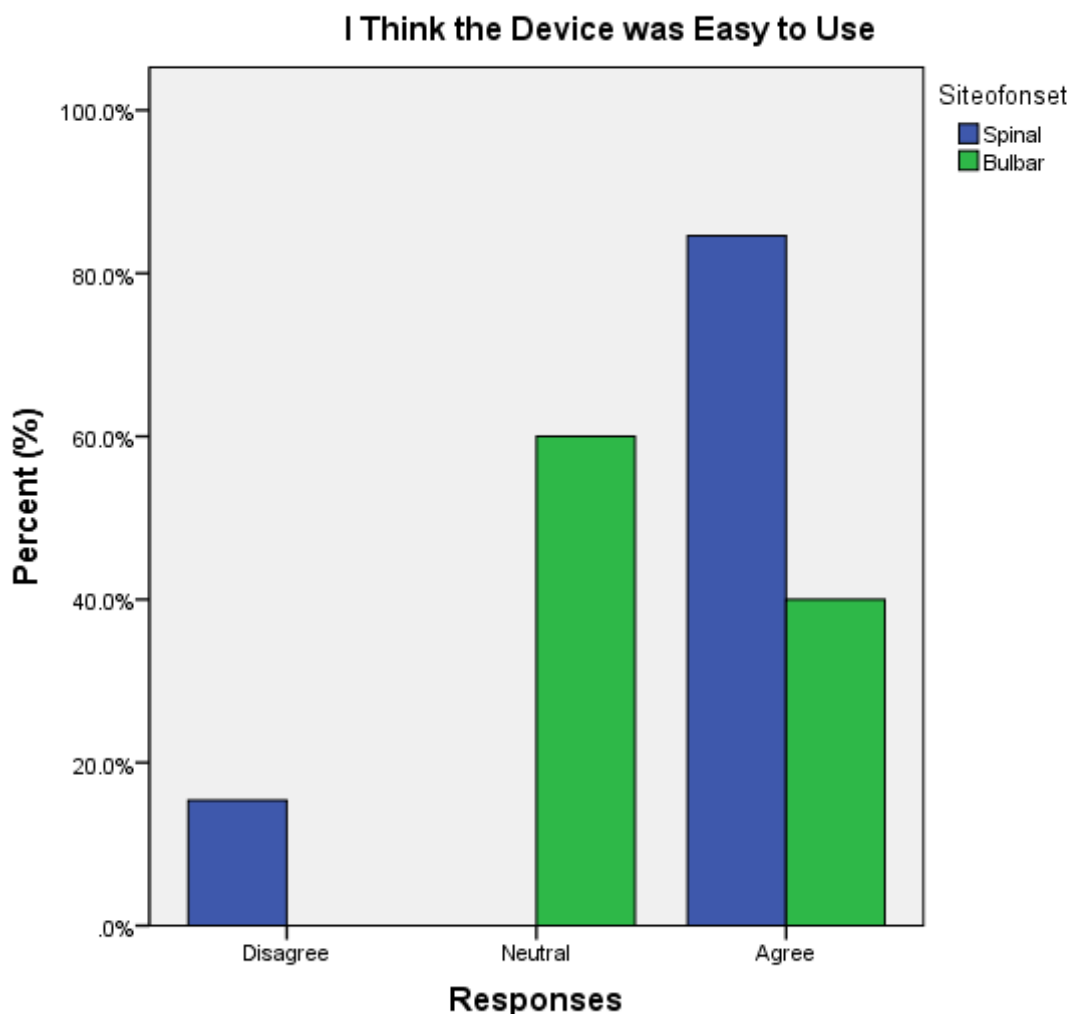


Figure 8.1: Bar Chart of Ease of Use Stratified by Site of Onset

8.5.5 Comfort

Twelve (66.7%) participants agreed and three (16.7%) participants disagreed that the devices were comfortable to use (Figure 8.2). A higher percentage of those using LVR (81.8%) agreed that it was comfortable to those using M-IE (42.9%). Similarly, a higher percentage of participants with spinal onset ALS (76.9%) agreed that the devices were comfortable to use compared to bulbar onset ALS (40%). One participant (7.7%) with spinal onset ALS and two participants (40%) with bulbar onset ALS disagreed that the devices were comfortable to use.

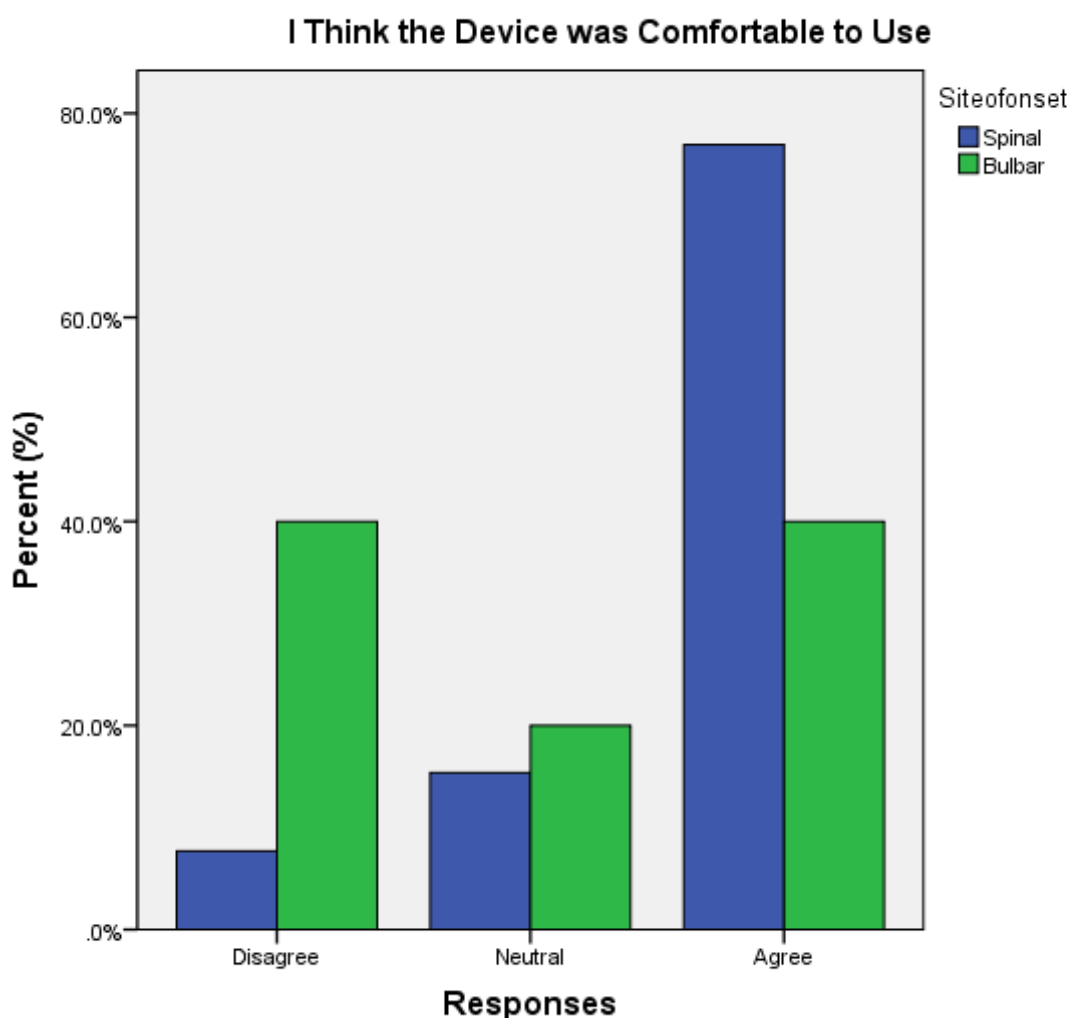


Figure 8.2: Bar Chart of Comfort Stratified by Site of Onset

8.5.6 Confidence

Twelve (66.7%) participants agreed and two (11.1%) participants disagreed that they were confident using the devices (Figure 8.3). A higher percentage prescribed LVR (72.7%) agreed that they were confident using LVR

compared to M-IE (42.9%). Two participants (18.2%) prescribed LVR disagreed that they were confident using the devices compared to zero participants prescribed M-IE. Spinal onset ALS (84.6%) was associated with a higher level of agreement of confidence using the devices compared to bulbar onset ALS (20%). One participant prescribed LVR and one participant prescribed M-IE disagreed that they were confident using the devices.

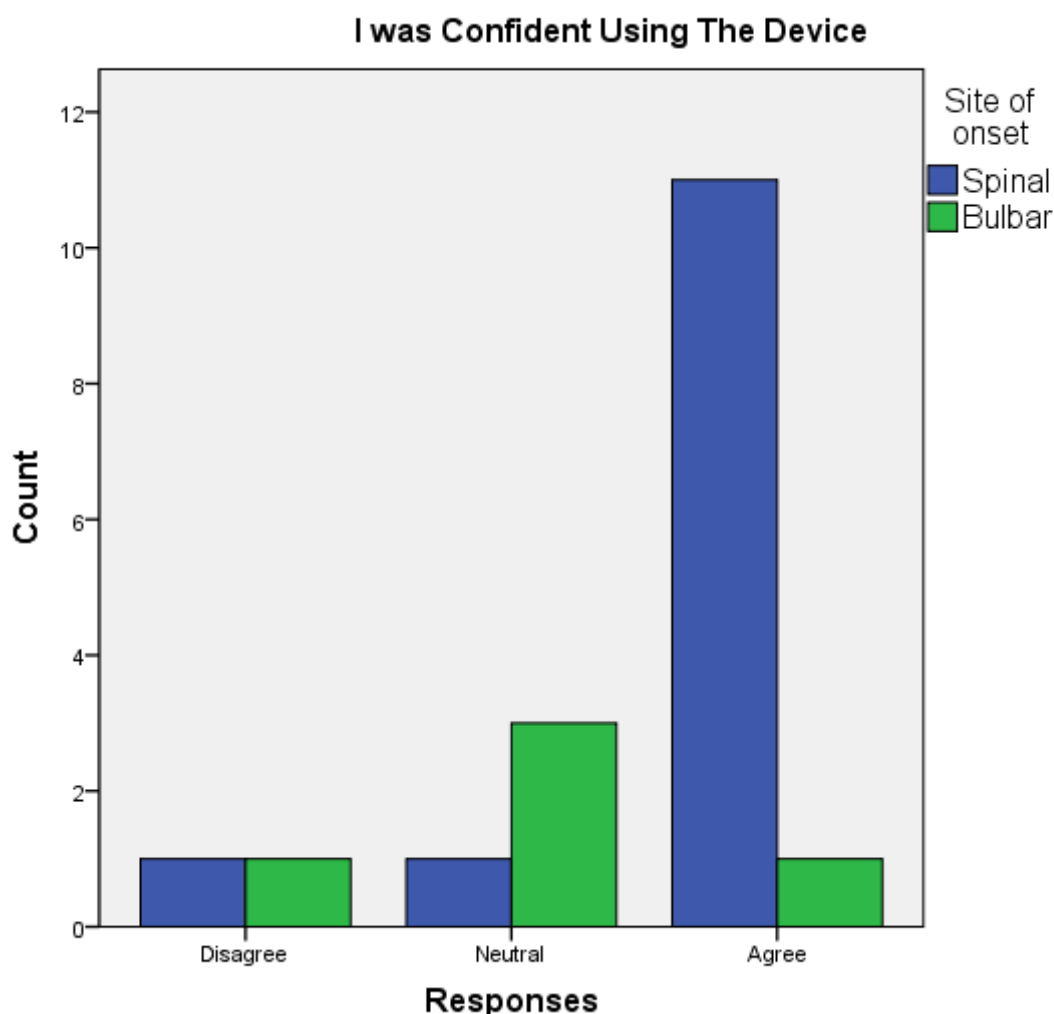


Figure 8.3: Bar Chart of Confidence Stratified by Site of Onset

8.5.7 Knowledge Leaving Clinic

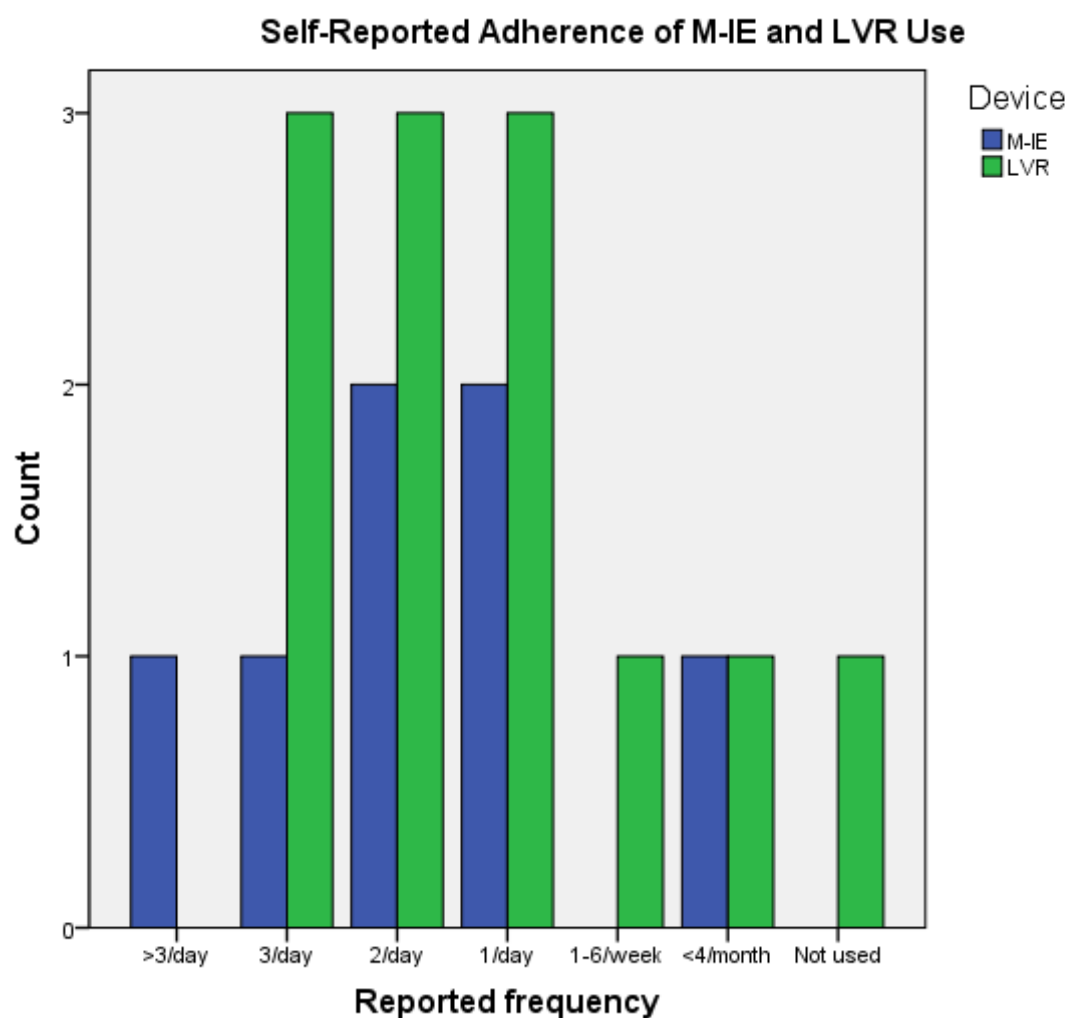
Seventeen (94.4%) participants agreed and one participant disagreed (5.6%) that they knew how to use their prescribed device when leaving the clinic. This one participant was prescribed M-IE and had spinal onset ALS. All participants prescribed LVR and all participants with bulbar onset ALS agreed that they knew how to use their prescribed device when they left the clinic.

8.5.8 Cleaning

Sixteen participants (94.1%) agreed and one participant (5.9%) neutrally responded that their device was easy to clean. All participants with spinal onset ALS and all participants prescribed LVR agreed that their device was easy to use.

8.5.9 Reported Adherence

There was a self-reported adherence rate of 94.7%. One bulbar onset ALS participant using LVR was non-adherent. All participants prescribed M-IE and all participants with spinal onset ALS reported using their device. The most common frequencies of reported use were once a day reported by five participants (26.3%) and twice a day reported by five participants (26.3%). A frequency of three times a day was reported by four participants (21.2%) and a frequency of greater than three times a day was reported by one participant (5.3%). Less frequent use of one to six times per week was reported by one (5.3%) participant and four times a month by one participant (5.3%). Frequency of use stratified by device and site of onset are illustrated in Figure 8.4 and Figure 8.5 respectively



M-IE=Mechanical Insufflation Exsufflation; LVR=Lung Volume Recruitment

Figure 8.4: Self-Reported Adherence of M-IE and LVR Use

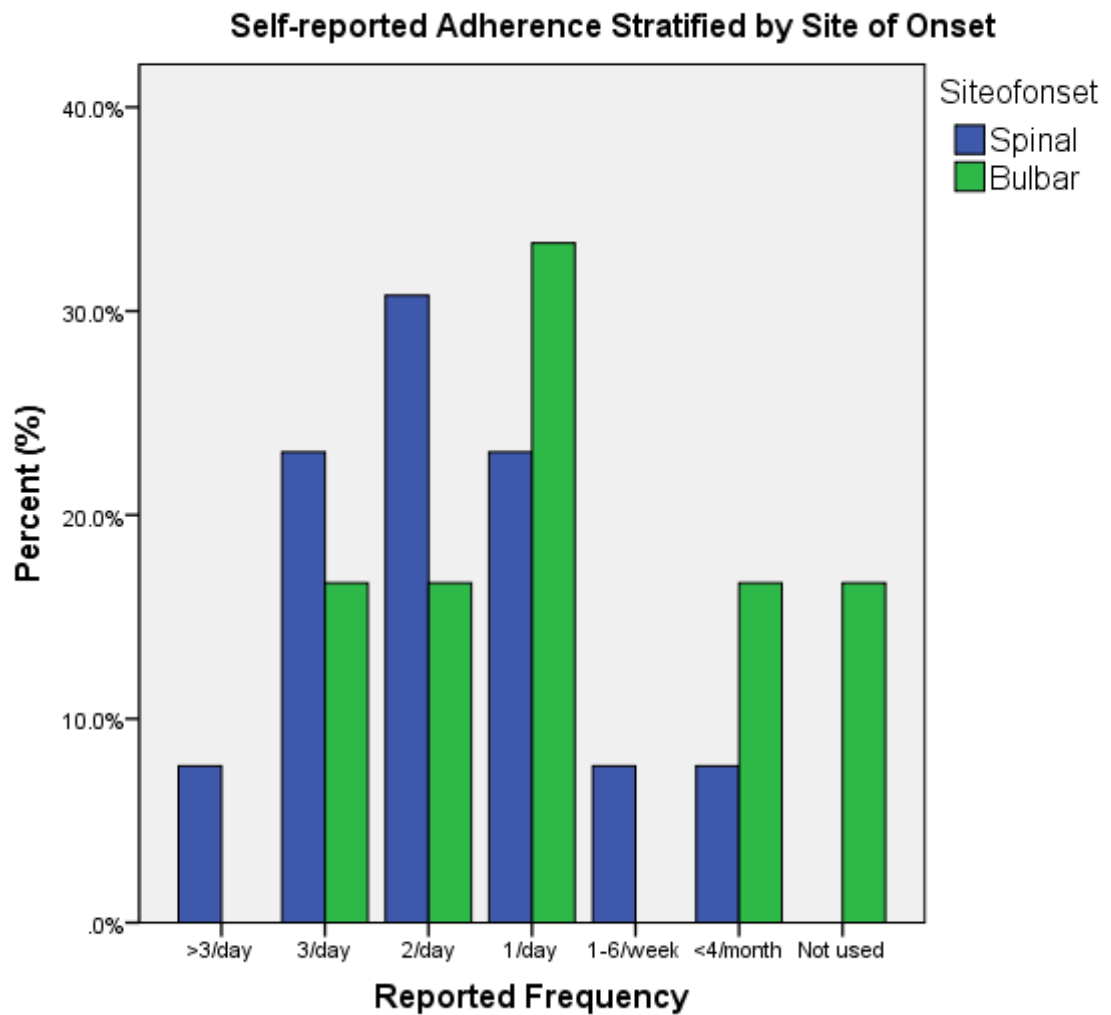
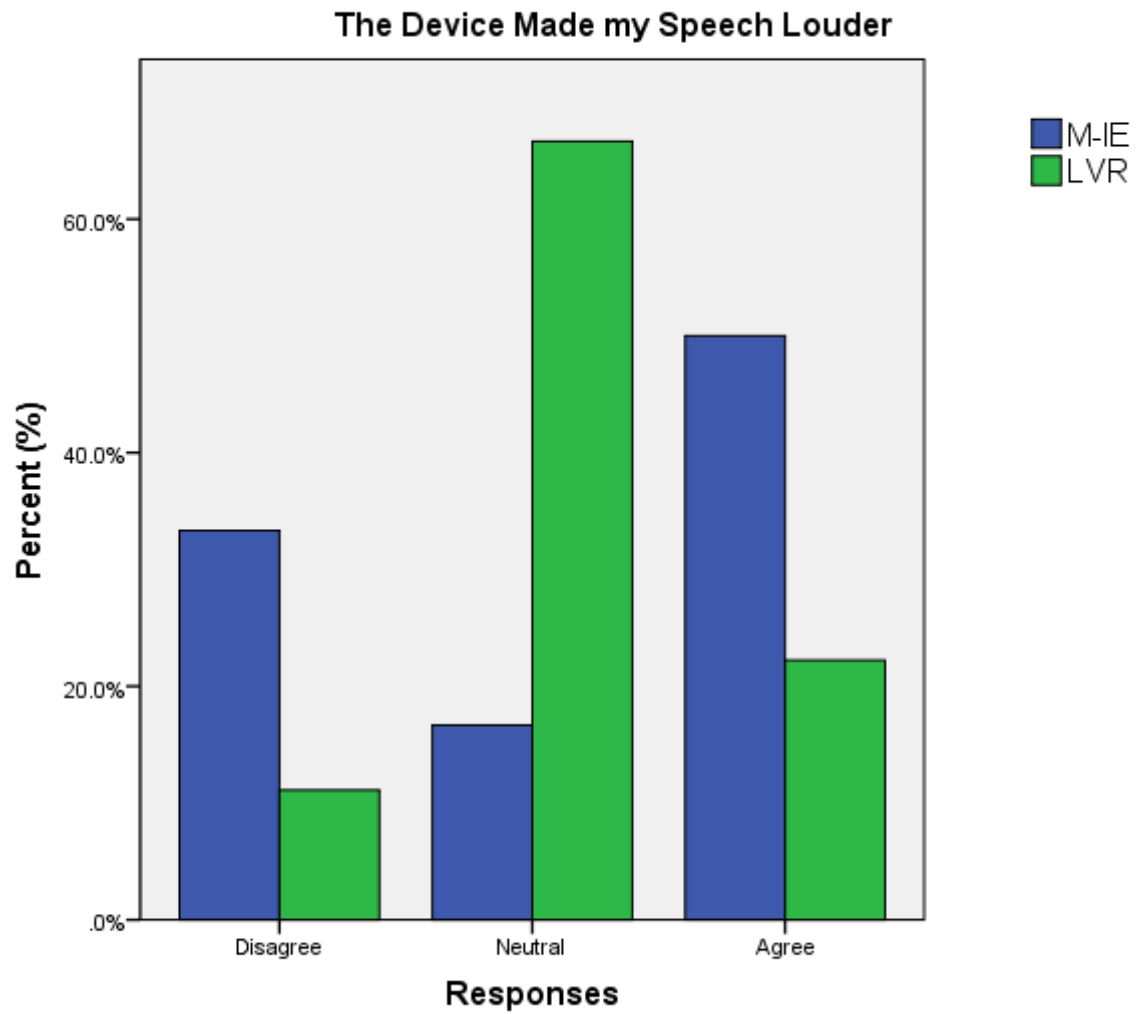


Figure 8.5: Self-reported Adherence Stratified by Site of Onset

8.5.10 The Self-Reported Effect of M-IE and LVR on Speech Volume

The self-reported effect of M-IE and LVR on speech volume was explored.

Of the 15 participants that answered this section, five (33.3%) agreed, seven (46.7%) had a neutral response and three (20%) disagreed that their device made their speech louder. Figure 8.6 and Figure 8.7 illustrates the participant's responses stratified by device and site of onset.



M-IE=Mechanical Insufflation Exsufflation, LVR=Lung Volume Recruitment

Figure 8.6: Self-reported effect of M-IE and LVR on Speech Volume

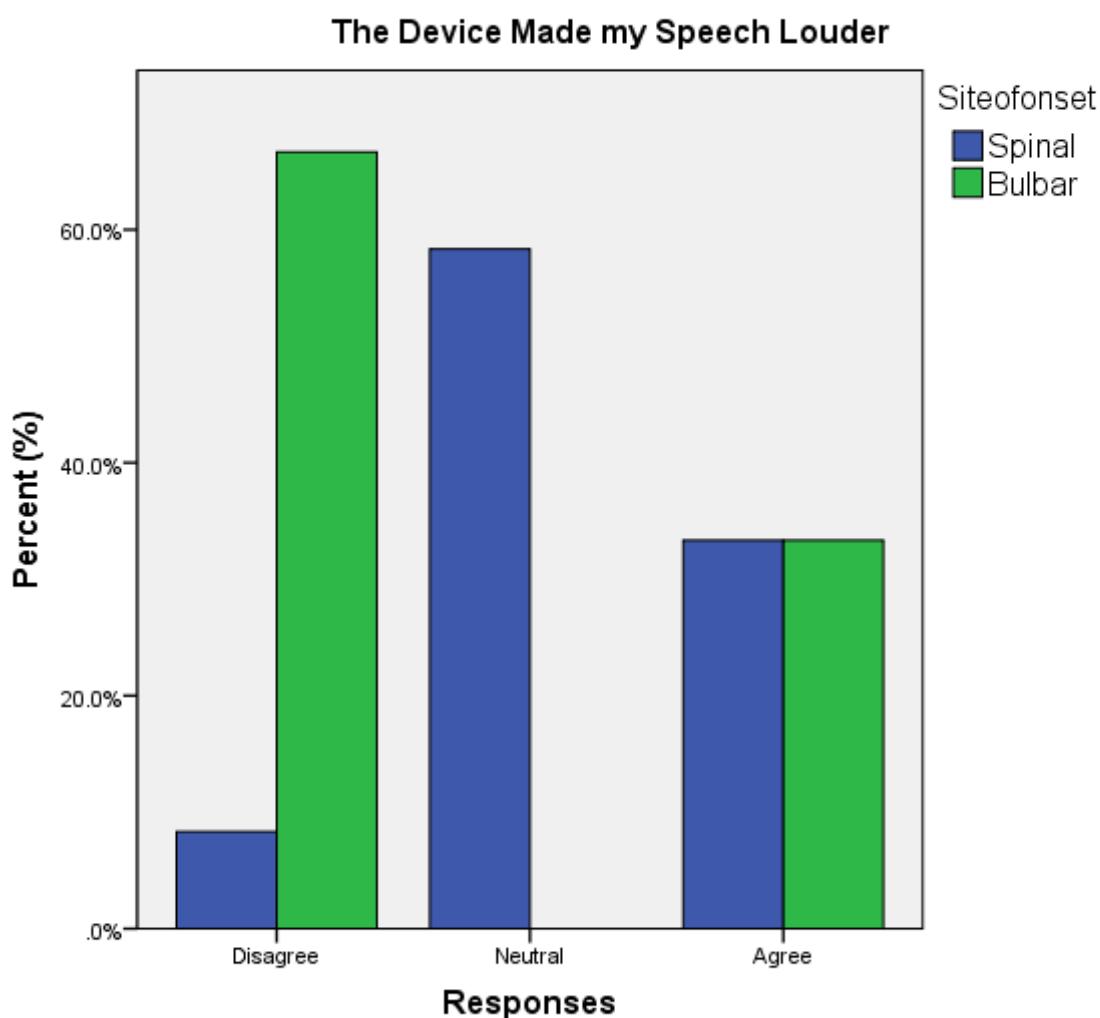


Figure 8.7: Self-reported effect of M-IE and LVR on Speech Volume Stratified by Site of Onset

8.5.11 The Self-Reported Effect of M-IE and LVR on Cough Strength

Ten (58.8%) agreed, five (29.4%) disagreed and two (11.8%) had a neutral response to the statement “The device made my cough stronger”. A higher percentage of 71.4% (n=5) participants who agreed were prescribed M-IE compared to 50% (n=5) who were prescribed LVR. Data was stratified into site of onset (Figure 8.8). Spinal onset ALS participants had a higher level of agreement of 66.7% compared to bulbar onset ALS with a 40% level of agreement. Bulbar participants also had a higher level of 60% (n=3) disagreement compared to spinal onset ALS participants that had a disagreement level of 16.7% (n=2).

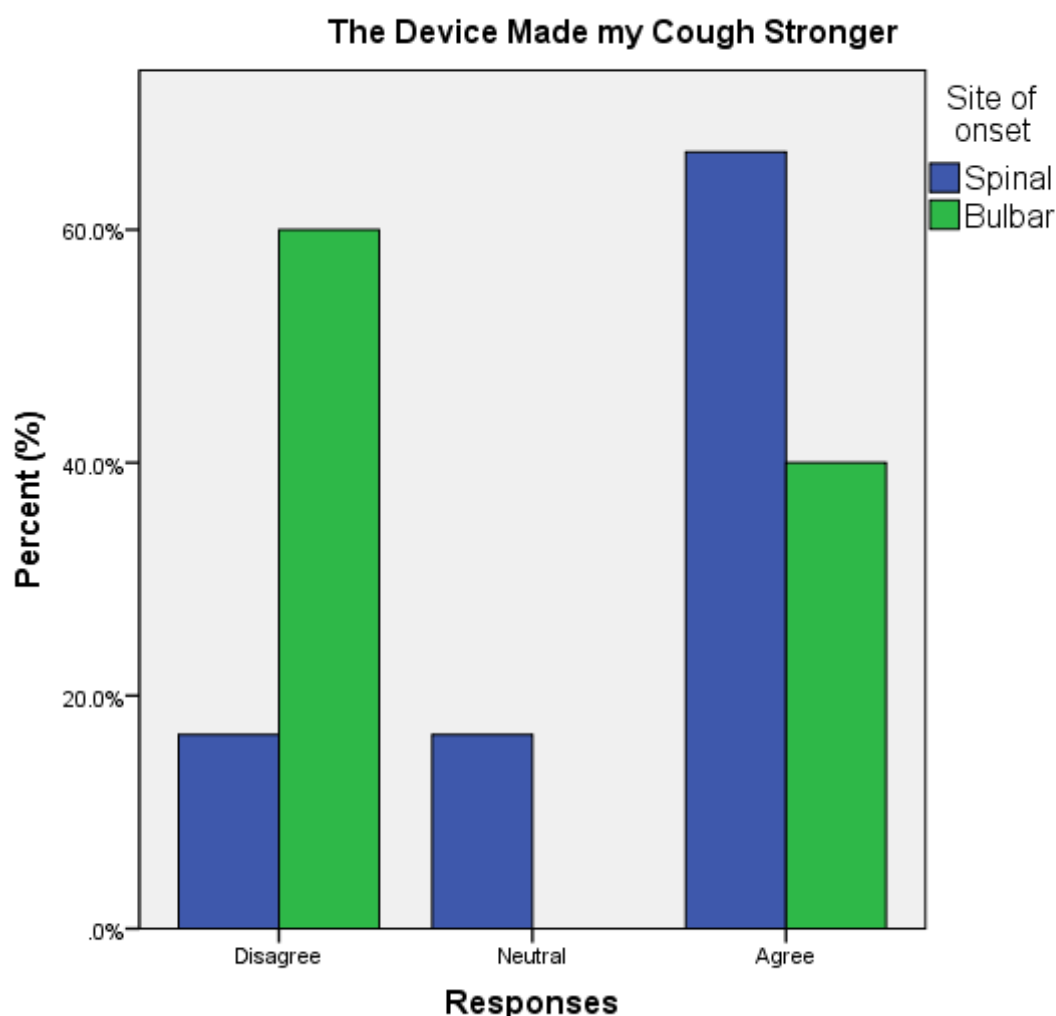


Figure 8.8: Self-Reported Effect of M-IE and LVR on Cough Strength Stratified by Site of Onset

8.5.12 The Self-Reported Effect of M-IE and LVR on Cough Strength During a Chest Infection

Two participants self-reported a chest infection after prescription of their device and completion of the questionnaire. M-IE was prescribed to one participant and they agreed that it made their cough stronger during a chest infection. The participant who was prescribed LVR did not report their experience of cough strength after their self-reported chest infection.

8.5.13 Participant Feedback

Additional feedback on their experience using LVR and M-IE was sought. Participants had the opportunity to comment further on their experience. The comments were categorised into positive and negative themes. Participants

provided feedback applicable to more than one theme. The themes and comments are outlined in Table 8.3.

Table 8.3: Participant Feedback on M-IE and LVR Experience and Usability

Positive Themes	
Theme	Device
Secretion clearance	
M-IE helped clear infection	M-IE
Very helpful. I know it is expanding my lungs.	LVR
M-IE helped clear infection	M-IE
Usability	
Easy for family member to use	M-IE
General	
M-IE has been excellent	M-IE
Found everyone very helpful and kind	LVR
Anything helps.	LVR
Negative Themes	
Interface	
Mask hurt bridge of nose	M-IE
Hurt nose	
Usability	
Patient elderly and unable to use alone.	M-IE
Did not feel comfortable using it as I could not remove it myself as I needed help using it	LVR
Pressures were too high. Did not use as a result. Felt throat was collapsing.	M-IE
Did not use during chest infection	LVR
Did not use device	LVR

M-IE=Mechanical Insufflation Exsufflation, LVR=Lung Volume Recruitment

8.6 Discussion

The questions addressed by the present study were to assess M-IE and LVR experience and usability; to measure self-reported adherence with M-IE and

LVR; to evaluate the self-reported effect of M-IE and LVR on cough strength and speech volume and to evaluate the self-reported effect of M-IE and LVR on cough strength during a chest infection. The main findings of the study indicate that M-IE and LVR were user friendly; there was a high level of adherence with M-IE and LVR use; M-IE and LVR were user friendly and M-IE and LVR increased self-reported cough strength. However there was a low level of agreement that the devices increased speech volume and the self-reported increase in cough strength during a chest infection is undetermined. The findings are discussed in detail below.

The majority of participants who were prescribed a device returned to clinic and completed the questionnaire. Three participants were unable to complete the questionnaire as they had passed away recently after receiving the devices. This indicates that M-IE and LVR were prescribed late in the disease process and highlights the role of M-IE and LVR with respiratory complications during end of life care in ALS. Participant experience and usability during end of life care would provide clinically relevant information but this could not be assessed.

This study shows that assistance for the administration of M-IE and LVR was required for the approximately half (52.6%) of ALS participants. This level of dependence was lower than 92% self-reported by adult and children NMD participants with the use M-IE (Mahede et al., 2015). The responsibility and the role a parent takes in the medical management of a child can explain this high level of assistance required with M-IE. The timing of the questionnaire in the study by Mahede et al. (2015) was not reported but could have influenced the adherence rates reported. This description of the level of assistance required by ALS participants provides an understanding of the care needs and clinical factors to be considered by prescribing clinicians.

Spinal onset ALS participants prescribed and overall LVR users required a higher level of assistance with the administration of their device compared to bulbar onset ALS and participants prescribed M-IE. Two reasons could explain the differences in the level of assistance. Firstly, a lower level of active participant participation is required with M-IE and could explain the associated lower level of dependence. The M-IE intervention is programmed

into the M-IE devices as determined by the prescribing physiotherapists. The participant places the mask over their face and the M-IE programme commences with the push of a button. In contrast, a higher level of participation is required with LVR. LVR requires the participant to actively compress the resuscitator bag and co-ordinate breaths with the bag compressions. Secondly, good upper limb function is also required for independent use of M-IE and LVR. Reduced level of upper limb function that is commonly present in spinal onset ALS (Chio et al., 2002) could explain the higher levels of assistance with spinal onset ALS.

The findings of this study would indicate that caregiver responsibility and possibly burden also increased in the carers of participants who required assistance with M-IE and LVR due to a higher level of disability associated with receiving a device. The introduction of a new medical device can mark a sign of progression of an illness (Moran et al., 2015) and a higher level of disability. Level of disability in ALS adds to caregiver burden (Burke et al., 2015). Motor weakness and behavioural and cognitive changes may have contributed to the 52.6% level of assistance in our study. Motor weakness is hallmark of ALS (Andersen et al., 2012). Patients with frontotemporal dementia were excluded from this study (Chapter 4.7.2). However, behavioural and cognitive changes can be present in up to 50% of patients with ALS (Mioshi et al., 2014, Ringholz et al., 2005). Reasons for level of dependence such as motor weakness, reduced upper limb function, a higher level of participation required with LVR and cognitive and behavioural changes were not explored in this study and can only be inferred.

The results indicate that M-IE and LVR were user friendly. Several statements with high levels of agreement support M-IE and LVR usability. There was a high level of agreement to the statements related to comfort, understanding how to use the device, ease of use, confidence and cleaning. This description of usability of M-IE and LVR among ALS participants which incorporates and confirms the separate observations of comfort of previous investigators (Senent et al., 2011) includes several new observations that provide a more complete understanding of the M-IE and LVR usability. There are possible reasons for a high level of agreement to the statements including clinical experience of the prescribing physiotherapists. Self-

reported knowledge of how to use both M-IE and LVR after leaving the ALS/MND MDT clinic was high. This ALS/MND MDT clinic reviews approximately 244 patients per year with one treating physiotherapist per clinic. Physiotherapy expertise and written patient information may have contributed to the high level of self-reported knowledge after prescription. The two physiotherapists working in this clinic have over ten years clinical experience each. Additionally, family and caregiver support present during the prescription of the devices could have contributed to this knowledge. However, the reasons for high levels of self-reported knowledge were not explored in this study and are only suggested.

A high level of self-reported adherence rate of 94.7% of M-IE and LVR was found in this study. Participants were adherent to both devices and a high number of participants also used it more than once a day. The adherence rate in this study adds to separate observations of previous investigators in ALS and NMD participants. Self-reported adherence rates of M-IE and LVR have been documented for ALS and NMD participants and range from 53% to 73% (Rafiq et al., 2015, Bento et al., 2010, Mahede et al., 2015). The difference in adherence rates in our study compared to those previously reported could be attributed to the challenges of accurately capturing self-reported measures (Yuen et al., 2013, Bollen et al., 2014) (Chapter 9).

Similar adherence rates between spinal and bulbar onset ALS participants were observed. However, non-adherence to M-IE and LVR associated with bulbar onset ALS has been reported (Rafiq et al., 2015). The findings reported in this cross sectional study do not confirm the association of poor adherence and bulbar onset ALS. In the RCT by Rafiq et al., (2015), poor adherence was related to severe bulbar impairment. Similarly, bulbar onset ALS was also associated with the poor adherence of NIV in a second RCT (Bourke et al., 2006). The survival benefits of NIV were associated with adherence of NIV of greater than four hours per night. The level of bulbar impairment was not evaluated in our study and our findings cannot be directly compared to the two RCTs mentioned above.

There is evidence to suggest there may be a role of M-IE and LVR to increase self-reported speech volume for some ALS participants. The results

indicate that there was a low level of agreement to the statement “The device made my speech louder” demonstrating that M-IE and LVR did not increase self-reported speech volume for the majority of participants but a total of five participants did agree to this statement. Self-reported effects of M-IE and LVR on speech volume were explored to determine if the increase of volume of air inhaled with M-IE and LVR would increase speech volume. It was assumed that low lung volumes had a negative impact on speech volume and larger lung volumes that are achieved with M-IE and LVR would increase speech volume. To date, the impact of M-IE and LVR on speech volume in NMD and ALS has not been described in the literature.

The results indicated that participants using M-IE and LVR increased self-reported increased cough strength. This is supported by the high percentage of agreement to the statement “the device made my cough stronger”. M-IE was more favourable than LVR in this regard. These findings add to the previous conclusions of Senent et al., (2011) who found that the self-reported effect of M-IE was rated higher than LVR. In this study, participants identified the device that created the highest Peak Cough Flow (PCF) more frequently than the therapists. Senent et al., (2011) recommended trialling different airway clearance devices to evaluate the participant’s self-reported efficacy to help guide prescription.

Spinal onset ALS participants prescribed and overall M-IE users reported a higher level of agreement of 71.4% and 66.7% respectively to the statement “the device made my cough stronger”. These are an interesting finding as the literature review in Chapter 2.7.4 identified that there was no trend among M-IE and LVR studies to determine if bulbar or spinal participants are affected differently by M-IE and LVR and it was unclear if one device is more superior to the other in ALS participants. One reason could explain this higher level of agreement in spinal participants. Firstly, bulbar onset ALS participants can have reduced laryngeal co-ordination. This prevents glottic closure and vocal cord adduction necessary for the compressive phase of cough. Cough strength can be reduced as a result of lower interthoracic pressures and limited isometric contraction of the expiratory muscles (Finder, 2010). The inability to participate in the compressive phase of cough compared to spinal onset ALS participants may explain this lower level of agreement.

Only two participants experienced a chest infection between the provision of a device and completing the questionnaire and only one of these participants responded to the question regarding cough strength during a chest infection. As a result the data collected was limited to one participant. This individual agreed that M-IE increased their cough strength during this chest infection. However, no conclusions regarding cough strength during a chest infection can be made. One study has evaluated the effect of M-IE and LVR on chest infection rates (Rafiq et al., 2015) and its effect remains unconfirmed. Although no statistically significant difference was found between the M-IE and LVR groups, the M-IE group had fewer days of chest infection symptoms.

A quantitative study design approach was undertaken for this study. The themes of the positive and negative comments were not explored to the extent that would be undertaken in a qualitative study. Interpretation of these comments is left to the reader. The comments may provide useful information for clinicians when they are considering prescribing a device to patients in a clinical setting. Our results indicate that M-IE and LVR have both positive and negative features. This is supported by the combination of negative and positive aspects of the participant's experience with M-IE and LVR revealed in the optional comments section (Table 8.3).

Negative comments featured structural components of the devices such as the M-IE and LVR mask. This was highlighted by two participants. The structural components of M-IE received negative criticism in respect to its size and weight in a study of NMD participants (Mahede et al., 2015). A further negative comment described a lack of control with the use of LVR. This highlights the level of assistance participants with ALS can require and the support that is essential for participants to avail of M-IE and LVR. This was further confirmed by 52.6% of participants who availed of help from a family member or carer to administer the device. However, one participant that was unable to use M-IE described it as very easy to use for family members.

The high pressure settings of the M-IE device self-reported by one participant influenced non-adherence. This participant had bulbar onset ALS.

Five LVR and five M-IE users in RCT (n=40) self-reported non-adherence to their devices as a result of severe bulbar dysfunction (Rafiq et al., 2015). This research cautions the use of M-IE in severe bulbar ALS who cannot protect their airway describing a risk of aspiration of saliva. A second study also cautions the use of M-IE in severe bulbar ALS due to a possible risk of dynamic upper airway collapse. Upper airway computed tomography scanning during the application of M-IE in three ALS participants including one with severe bulbar dysfunction with the use of M-IE was performed. The exsufflation phase showed a closing of the nasopharynx, retraction of the uvula, and a reduction in the diameter of the oropharynx. The participant with severe bulbar dysfunction had the greatest narrowing (Sancho et al., 2004). Positive comments described the devices as valuable in clearing a chest infection and expanding lungs. Positive features revealed in the qualitative study of M-IE in NMD children included a greater ability to manage a child's health (Moran et al., 2015). This theme is reflected in our study in the above positive comments. Both the positive and negative findings add to the limited evidence of the participants experience and usability of M-IE and LVR in ALS.

8.7 Limitations

Limitations of this study exist in respect to three areas; questionnaire methodology, timing of the questionnaire, limited qualitative analysis and small population size.

Firstly, the limitations of this study are characteristic of a questionnaire methodology that is not validated and does not have any historical or comparative data. The questionnaire was developed due to limited published evidence on the usability and self-reported benefits experienced by ALS M-IE and LVR users. As a consequence, the results of this study cannot be directly compared to other published research. Self-reported responses have their own individual limitations including response bias, socially acceptable answers, under and over reporting (Bollen et al., 2014, Yuen et al., 2013). In addition the five point Likert scale utilised is one-dimensional limiting choices to one of five options.

Secondly, long term evaluation of participant experience was not evaluated. This study provides an initial evaluation of participant experience and usability with M-IE and LVR. The questionnaires were completed on average 60.4 days after prescription of M-IE and LVR. This was endeavoured to maximise data collection. This time frame is accurate to indicate safety when exploring areas such as knowledge of how to use the device and cleaning of the device that indicate safety. Areas such as adherence and level of dependence may change over time.

Thirdly, the themes generated to describe participant experience were not generated in a strong qualitative manner.

Finally, further limitations to this study are features of statistical challenges attributed to small participant numbers.

8.8 Recommendations

Prescribing clinicians can be confident that M-IE and LVR are user friendly for both spinal and bulbar onset ALS participants. Clinicians must be aware of the home care in place prior to prescription to establish if adequate support is in place to maximise adherence and to be aware of possible increase in caregiver burden. M-IE and LVR may not increase self-reported speech volume but it may be prescribed to increase self-reported cough strength.

Further research should focus on the impact of M-IE and LVR on long term experience and usability and caregiver burden in the form of quantitative and qualitative studies. Larger studies should assess the degree of bulbar dysfunction to further evaluate the impact of site of onset on adherence. In addition, electronic adherence monitoring of M-IE and LVR would provide accurate adherence rates (Chapter 9).

8.9 Conclusion

In summary, this study has identified that ALS participants have a positive experience with M-IE and LVR use and M-IE and LVR are user friendly. Participants are mostly adherent with M-IE and LVR and M-IE and LVR increase self-reported cough strength. In all cases there was a high level of agreement. Self-reported increase in cough strength during a chest infection

is undetermined because of a low number of chest infections experienced. M-IE and LVR may play a role in increasing self-reported speech volume for some ALS participants. These findings add to the limited research of participants experience with airway clearance devices in NMD (Moran et al., 2015, Mahede et al., 2015) and ALS participants (Senent et al., 2011).

Chapter 9: Development of a Prototype to Measure Adherence to Lung Volume Recruitment

9.1 Introduction

This chapter will describe the initial development and testing of an electronic prototype to measure adherence in Lung Volume Recruitment (LVR).

9.2 Literature Review

The World Health Organisation, (2003) has defined adherence as “the extent to which a person’s behaviour – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider”. Accurate measurement of adherence is essential to guide medical and physiotherapy interventions to attribute outcomes to the prescribed interventions, such as medication or exercise. It is well documented that poor medication adherence has a negative impact on disease outcome (Osterberg and Blaschke, 2005). Poor adherence negatively affects medical services’ resource management and impacts negatively on patient Quality of Life (QOL). Poor adherence is common in chronic conditions such as diabetes, hypertension and asthma (Williams et al., 2004).

Approaches to measuring adherence include subjective and objective ratings of adherence. Subjective measures include self-report and patient administered questionnaires. Objective measures include remaining dosage units and electronic medication event monitoring systems. The expense of electronic measures limits their wide use (WHO, 2003).

Self-reported measures are susceptible to misrepresentation. Over reporting (Arnsten et al., 2001) and underreporting are common (Lu et al., 2008) in medication use when compared to electronic monitoring. Self-reported measures of exercise have also been compared to electronic monitoring. One such study compared the duration and frequency of Wii fit exercise reported in an exercise log to the electronic recording on the Wii hard drive for a 10 week home based exercise programme (Yuen et al., 2013). The duration of exercise was over reported and the frequency was under reported. The author’s concluded that caution should be taken when using an exercise log to measure exercise behaviour.

A systematic review of the available self-report measures and their psychometric properties of unsupervised home based exercise was evaluated (Bollen et al., 2014). A total of 61 methods of self-report measures were identified. Self-reported measures included questionnaires, logs, visual analogue scales and a tally counter. One component of psychometric testing was performed on two self-reported measurements only. There is no gold standard for self-report measures in unsupervised exercise programmes. A self-report measure that is validated and reliable is necessary.

Adherence to cough adjunct devices in Neuromuscular Disease (NMD) and Amyotrophic Lateral Sclerosis (ALS) participants was described in Chapter 8. Adherence to Mechanical Insufflation Exsufflation (M-IE) ranged from 47.6% (Bento et al., 2010), to 59% (Rafiq et al., 2015) and 73% (Mahede et al., 2015) in NMD and ALS participants. Adherence to LVR was reported as 71% in ALS participants (Rafiq et al., 2015). In all of these studies adherence was recorded by self-report measures. A self-administered paper based questionnaire was completed in one study (Mahede et al., 2015) and participants completed a diary in a second (Rafiq et al., 2015). The third study, did not describe the self-report method undertaken (Bento et al., 2010). The subjective methods utilised to record adherence suggest that the wide range of reported adherence rates in the above studies may be inaccurate.

The factors that influence adherence to M-IE and LVR have not been explored. However, Rafiq et al., (2015) highlighted that five out of the six non-adherent participants to LVR had severe bulbar dysfunction, which suggests that the adherence in this subgroup requires investigation.

Self-report measures of adherence to a medication or exercise are often not accurate (Williams et al., 2004, Yuen et al., 2013, Bollen et al., 2014).

Adherence to M-IE and LVR studies in ALS and NMD participants varies dramatically (Mahede et al., 2015, Bento et al., 2010, Rafiq et al., 2015). The methods that assessed adherence in these studies are poorly documented and have no evidence of psychometric property testing. The studies are likely to have formed inaccurate adherence rates as a result of the lack of standardised measures implemented.

It is possible to retrieve a patient's history of M-IE on an M-IE device but it is not possible with a LVR device. Accurate measures of LVR adherence are warranted. Reliable evaluation of LVR use would provide clinicians and researchers with knowledge to interpret LVR interventions accurately. Positive outcomes with adherence of a LVR device would also provide evidence to support continued use of the device in a financially burdened health care system. A LVR adherence prototype was developed to meet these clinical needs.

9.3 Methodology

9.3.1 Study Design

This study had two aims. The first aim was to design and build an electronic prototype device that would measure adherence to LVR. The second aim was to investigate the sensitivity of this LVR adherence prototype.

The objectives were to:

1. Design and build a LVR adherence prototype suitable for laboratory testing
2. Measure the sensitivity of the electronic adherence prototype

9.3.2 Setting

No patients were involved in this laboratory based study. The lead researcher and academic supervisors completed all trials.

9.3.3 Ethical Considerations

Ethical approval was not sought as this study did not involve patient participation.

9.3.4 Study Personnel

The design, build and testing of the prototype device was led by the principal investigator. Individual members of the research team contributed as follows:

Principal Investigator: Lead member of the team, main advisor and co-developer of the device, participated in the sensitivity trials and the analysis of the results.

Supervisor: Idea of device and participated in the sensitivity trials.

Co. Supervisor: Advice on device measurement parameters and participated in the sensitivity trials.

Engineer: Construction and design the LVR device. Hardware development, software development and testing.

9.3.5 LVR Adherence Prototype Construct

The LVR adherence prototype was developed during a summer internship jointly funded by the 3U partnership and Research Motor Neuron Disease. The 3U partnership creates educational opportunities between Royal College of Surgeons in Ireland, Dublin City University and Maynooth University.

The basic concept of the adherence prototype is as follows: The one way valve facemask of a standard LVR device was modified (Figure 9.1). Motion and pressure sensors were inserted into the facemask. Motion of the prototype “woke” the device so that it would become available to record time stamps. A time stamp was recorded if there was sufficient compression of the facemask. This was to replicate ALS patient usage. After 30 seconds of inactivation, the prototype returned to a sleep mode to conserve battery life.

The construction of prototype is described in detail in the engineers report (Appendix 12). This includes the hardware materials used, details about the firmware, construction of the prototype and analysis of trial data.

9.3.6 Prototype Trials

One prototype was constructed and a new facemask was attached to the prototype for each new trial to minimise the risk of cross contamination of possible infections.

Each tester was instructed to perform LVR similar to that of an ALS patient. In a clinical setting patients are instructed to use LVR between one and three times a day or as required. The LVR bag is compressed a number of times to stack breaths until a Maximum Insufflation Capacity (MIC) is achieved (Chapter 2.7.2). Commonly 3–5 breaths are required to achieve MIC. A standard LVR treatment cycle includes 3–5 cycles of MIC followed by a cough. The tester documented each LVR intervention and duration. The tester also documented any purposeful non-LVR movement of the prototype by the tester (for example if another individual picked up the device, or if it

was dropped or moved location). This was to ensure that any non-LVR activity could be identified and distinguished from LVR activity. The LVR prototype was then returned to the engineer and data were extracted from the software and analysed. The prototype was then attached to a new mask in preparation for the next trial, which was trialled with another tester.

9.4 Statistical Methods

Analysis of the duration and frequency of the time stamps were filtered by the electrical engineer. Non-LVR activity was distinguished and identified from LVR activity. The filtered data was entered into Microsoft Excel and analysed using SPSS (IBM SPSS Statistics 23). Crosstabulation was used to calculate sensitivity.

9.5 Results

Figure 9.1 and Figure 9.2 depict the adapted face mask and the completed LVR adherence prototype.

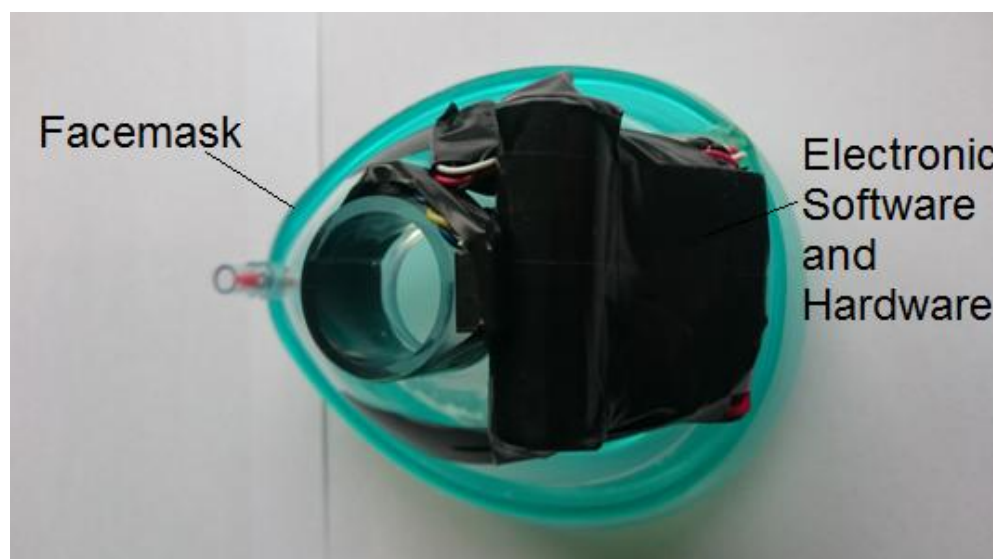


Figure 9.1: Adapted Facemask and Attached LVR Adherence Prototype Electronic Software and Hardware



Figure 9.2: Complete LVR Adherence Prototype Electronic Software and Hardware

Table 9.1 outlines the interventions completed by the three testers. A total of 252 time stamps were recorded by the three testers over six days, five hours and 36 minutes. A sensitivity of 97.2% was calculated. No adverse events were experienced by any of the testers.

Table 9.1: Tester Interventions

Tester	Duration of Trial	Number of Inhalations per Cycle	Total Number of Cycles
Tester 1	2 days	1	5
Tester 2	6 days	3	14
Tester 3	4 days	3-8	26

9.6 Discussion

This study demonstrated that a LVR adherence prototype could potentially be developed commercially in order to accurately measure LVR adherence. The first aim of this study was to construct a LVR adherence prototype. This was successfully accomplished by the electrical engineer in consultation with the lead researcher and academic supervisors. The second aim of this study was to measure the sensitivity of the electronic adherence prototype. The findings from the limited data collected from the small sample size of three testers indicated that the prototype was sensitive.

Accurate measures of adherence are paramount to any medical intervention to accurately assess outcome and guide treatments. As described earlier in the chapter, the non-adherence of medications in chronic conditions such as asthma, diabetes and hypertension place a huge demand on resources and negatively impact patient outcomes (Williams et al., 2004, Osterberg and Blaschke, 2005). Self-report measures are commonly utilised to measure adherence but their use has major limitations. For example in physiotherapy no gold standard for self-report measures exists to accurately assess unsupervised exercise programmes (Bollen et al., 2014).

A LVR adherence device would be suitable for both research and clinical purposes. Currently no sufficiently large Randomised Control Trial (RCT) of M-IE and LVR exist in any population. An RCT comprising of M-IE, LVR and control groups is required to comprehensively evaluate the outcome in ALS patients. Although a Cochrane review concluded that there was insufficient evidence to support or not support the use of M-IE in NMD participants (Morrow et al., 2013), airway clearance devices such as M-IE and LVR are recommended for use in NMD and ALS (Bott et al., 2009, Miller et al., 2009a, O'Callaghan et al., 2014, NICE, 2016). In an RCT of LVR and MIE, adherence to each device could be accurately recorded allowing intention to treat analysis of the data.

In the study by Rafiq et al., (2015), severe bulbar dysfunction was associated with non-adherence of 23.8% of the LVR participants. A sensitive LVR adherence device will not only provide accurate adherence monitoring but it would also help determine the predictors of adherence and non-adherence.

This LVR adherence device is in the very early stages of development and the trials to measure sensitivity are for the purposes of reporting in this thesis only. A comprehensive certification process is required before it can be considered for a clinical or a research setting. Despite the foreseeable challenges associated with this process the LVR adherence prototype was affordable to develop. Components cost a total of €128. This is an affordable amount that could be allocated to a clinical trial budget in the future.

9.7 Limitations

Limitations were encountered during the construct and assessment of the LVR adherence prototype. Firstly, the one way valve LVR facemasks were modified for the purpose of the prototype and subsequent trials. The modified mask could be considered cumbersome. Secondly, the trials were of short duration. The device would be reviewed approximately every three months in a clinical or research setting. The three trials were not completed for this duration. Thirdly, the trials undertaken were not completed to calculate the specificity of the device. Finally, the data used to calculate the sensitivity of the device was limited with a total number of three testers and results are therefore limited on the basis of a very small sample and further investigation of sensitivity is warranted.

9.8 Considerations for Future Research

It is expensive and time consuming to develop a safe and regulated medical device suitable for clinical and commercial use. Prior to this, the adherence prototype components must be assessed for safety, hygiene and usability in a clinical and research setting. The structure of the device is large and it is not water tight. Smaller water tight hardware would be more suitable for participant use to ensure adequate hygiene standards are maintained. Longer trials are required to collect statistical evidence to support the efficacy of this LVR adherence device if the device is considered for use clinically or in clinical trials. Further research must also be carried out to determine the marketing potential for this device. Uses in applications beyond ALS research must also be explored.

9.9 Conclusion

This chapter has detailed the construction and initial sensitivity testing of a LVR adherence device. A LVR adherence prototype can be developed and it can measure LVR adherence accurately. Longer studies investigating long-term use of a LVR electronic adherence device would further confirm the sensitivity and specificity of the prototype in a clinical situation. This device has potential to be used in a clinical setting, in clinical research and possibly other marketable areas.

Chapter 10: Overview and Conclusions of the Thesis

10.1 Introduction

This thesis presented novel research in the area of respiratory management of Amyotrophic Lateral Sclerosis (ALS) over three studies. Three studies were formulated and presented on the basis of five main aims. The first was to prospectively measure respiratory muscle strength and function, physical function and outcome in an Irish ALS cohort over one year. The second aim was to examine prescription practices in relation to Mechanical Insufflation Exsufflation (M-IE) and Lung Volume Recruitment (LVR) devices and to compare the above characteristics in those who were prescribed such devices and those who were not. The third was to evaluate the experiences of participants who were prescribed M-IE and LVR. The fourth aim was to design and build an electronic prototype device that would measure adherence to LVR. The final aim was to investigate the sensitivity of this LVR adherence prototype. Original research is presented in the areas of the rates of decline of respiratory and functional measures, the clinical practices of M-IE and LVR prescription and the participants experience and usability of M-IE and LVR. Finally, a unique electronic LVR adherence device was created.

10.2 Overview of the Thesis

A comprehensive literature review that described ALS and critiqued the available literature of M-IE and LVR in this population was detailed in Chapter 2. A lack of understanding of the long term changes of respiratory muscle strength, function and morbidity, cough strength and outcomes associated with M-IE and LVR and the clinical practices and the ideal time to prescribe M-IE and LVR were identified. These findings formulated the aims and objectives of the prospective observational cohort study described in Chapter 4. Chapter 3 justified the outcome measures employed within this one year prospective study including Sniff Nasal Inspiratory Pressure (SNIP), Peak Cough Flow (PCF), Slow Vital Capacity (SVC) percent predicted and Amyotrophic Lateral Sclerosis Functional Rating Scale Revised (ALSFRS-R). The methods undertaken to complete this study are detailed in Chapter 4. Chapter 5 reports the findings of the prospective study that included 108 participants. The findings from this study identified that SNIP, PCF, SVC percent predicted and ALSFRS-R declined significantly ($p < 0.001$) at a rate of

18.72cmH₂O, 124.84L/min, 17.49% and 9.62 units per year respectively. One third reported a chest infection and 19.44% died. Participants prescribed a device had significantly lower average SNIP, PCF, SVC percent predicted and ALSFRS-R ($p<0.001$); site of onset, time from diagnosis was not significantly different to participants not prescribed a device. The results and how they contributed to the literature of M-IE and LVR in ALS are discussed in Chapters 6 and 7. This contribution included the first reported rate of decline in SNIP, PCF, SVC percent predicted in an Irish ALS cohort. In addition, device prescription was detailed for one Irish ALS clinic, providing a point of reference for clinicians and future trials.

Chapter 8, a complete second study detailed the quantitative analysis of experience and usability of M-IE and LVR in ALS and concluded that participants had a positive experience with M-IE and LVR use. M-IE and LVR were user friendly and they may play a role in increasing self-reported speech volume for some ALS participants. Participants were mostly adherent with M-IE and LVR. Finally, M-IE and LVR increased self-reported cough strength but self-reported increase in cough strength during a chest infection could not be determined due to limited data.

The final study, the development of an electronic LVR adherence prototype and its associated sensitivity is described. This chapter detailed the construction and initial sensitivity testing of a LVR adherence device in initial short trials. This study concluded that the device has potential to be used in a clinical setting, in clinical research and possibly other marketable areas. However, longer studies investigating long-term use of LVR would further confirm the accuracy of the prototype in a clinical situation.

10.3 Limitations of the Thesis

Limitations exist in respect to each individual study. Methodological challenges were the primary limitations in the prospective study. This included an unequal number of measurements per participant, a low number of measurements performed in a number of participants, an unbalanced follow-up and an incomplete analysis of an ALS cohort. The questionnaire methodology, timing of the questionnaire and small population size are limitations of the experience and usability of M-IE and LVR in ALS study.

Structural and technical limitations of the electronic LVR adherence device study included the large size of the modified facemask and the inadequate length of trial duration for clinical use. The final limitation applies to prospective and the experience and usability of M-IE and LVR in ALS study. All participants were recruited from one Irish ALS/Motor Neuron Disease (MND) Multidisciplinary Team (MDT) clinic. Therefore, clinical management may not be transferable to other clinical settings as practices may vary.

10.4 Recommendations for Future Research

The areas for further development include a large scale Randomised Control Trial (RCT) to determine the efficacy of M-IE and LVR, a study to determine the optimum time to commence airway clearance strategies, a longer term evaluation of experience, usability and caregiver burden with the use M-IE and LVR in the form of qualitative and quantitative methods in ALS. Finally, a longer duration study to investigate long-term use of the electronic LVR adherence device would provide further confirmation of the accuracy of the prototype in a clinical situation.

10.5 Conclusion

This thesis has provided new knowledge in a number of areas. Rates of decline in SNIP, PCF and SVC percent predicted in an Irish ALS cohort were established. A point of reference for future studies and for physiotherapists to guide their clinical practices has been provided by the novel comprehensive research into the frequency of M-IE and LVR prescription and the participant's characteristics at the time of M-IE and LVR prescription in ALS. This thesis has also presented the participants experience and usability of M-IE and LVR, an area that is deficient in ALS literature to date. Finally, the electronic LVR adherence device has the potential to be used in a clinical setting, in clinical research and possibly other marketable areas.

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Appendices

Appendix 1: ENCALs Respiratory Outcome Measure Standard Operating Procedure

Respiratory Measures ALS

ENCALS SOP

Index

Background.....	1
SVC and FVC TESTING	2
Clarification of used terms:	2
Step 1) Preparation.....	2
Step 2) Calibration	2
Step 3) Adjusting the set-up menu.....	3
Step 4) Explaining the test.....	3
Step 5) Instructions for the subject during the test.....	4
Step 6) Processing of the measurement outcomes	4
Additional Guidelines	5
Care and cleaning of device	5
SNIP TESTING	6
Clarification of used terms:	6
Step 1) Calibration	6
Step 2) Explaining the test.....	6
Step 3) Asking for patient's information	6
Step 4) Preparing the test.....	7
Step 5) Performing the test	8
Additional Guidelines	8
Care and cleaning of device	8
References.....	9

Background

Vital capacity (VC) is one of the core outcome measures routinely used in ALS clinical trials. Therefore, accuracy and repeatability of VC measurements are essential to obtain reliable efficacy data in randomized ALS clinical trials. VC is defined as the volume of air expelled during expiration following a full inspiration and completed while the patient is as relaxed as possible while completing the expiration [1, 2]. Acceptable VC test quality requires optimal patient performance. Optimal patient performance requires adequate coaching.[3, 4]

During this training we will focus on Forced vital capacity (FVC), Slow vital capacity (SVC) and Sniff nasal inspiratory pressure (SNIP).

Step 3) Adjusting the set-up menu

Your test conditions need to be set on the spirometer.

- Turn the machine on by pressing the on/off button.
- Select the test you would like to perform: SVC (shown as Relaxed Spirometry) or FVC (shown as Forced Spirometry).
- Report the patient's:
 - sex, select by dropdown menu: male or female
 - race*, select by dropdown menu.
 - height, fill in the height, units are country-specific
 - weight, fill in the weight, units are country-specific (optional)
 - age, fill in the age in years

After you have filled in the patient's information, press 'finish'.

The image shows a 'New Patient' form. At the top, there is a title bar that says 'New Patient'. Below it, there is a section titled 'Patient Details'. This section contains several fields: 'ID' (a yellow box), 'Last Name', 'First Name', 'Sex' (a dropdown menu with 'Male' selected), 'Origin' (a dropdown menu with 'Caucasian' selected), and 'Height (cm)'. Below these fields is a numeric keypad with digits 1-0 and a decimal point. To the left of the keypad is a blue arrow pointing up. To the right of the keypad is a blue arrow pointing right. At the bottom of the form, there are two buttons: 'Cancel' and 'Finish'. In the bottom right corner, there is a battery icon and the time '10:16'.

Step 4) Explaining the test

General: "Your breathing capacity (how much air you can push in and out of your lungs) will be tested using the vital capacity test (VC). The VC measures the maximum amount of air you can exhale (blow out) following a deep breath. The spirometer will measure how much air you have exhaled. This test will be done 3 times to ensure that we have measured your best attempt."

- SVC specific; "Please start with normal breathing. After a few breaths, I want you to fill your lungs completely, then blow out gently all the way until you are empty.[3]"
- FVC specific; "Please start with normal breathing. Then I want you to take a huge breath in until your lungs are completely full, and blast it out as hard and as fast as you can until you feel you are completely empty and cannot blow out further.[3]"

Make sure the subject has a complete understanding of the test!

Step 5) Instructions for the subject during the test:

General: During testing, the Research(er) (Nurse) should exhibit enthusiasm, allay the patient's anxiety, convey simple instructions, demonstrate each test, give vocal encouragement and provide feedback on performance. Observe the patient's nonverbal cues, such as facial expressions and body language, and use your own body language effectively. This can enhance the patient's test performance [3, 4].

The patient could be distracted by people surrounding him/her during performance of the VC test. Before you start the measurement, agree with the patient if he/she want(s) to perform the test alone so that he cannot be distracted by people around him.

Positioning: Make sure the patient sits upright with the legs next to each other, shoulders pulled back and eyes wide open.

Placing mask or mouthpiece:

Clear of any saliva and place the mouthpiece in the patient's mouth and place nose clip on the nose making sure the patient can seal their lips around the mouthpiece and that no air is leaking. Or place the mask over the nose and mouth of the patient, supporting it firmly behind the head.

- SVC specific;

- "Please start with normal breathing. After a few breaths, I will ask you to take as big a breath in as possible to fill your lungs."

- Say, "I want you to breath in as deeeeeeep as possible." Then say, "Deeper."

- "blow out gently, all the way until you are empty." A tactile cue, such as placing a hand gently on the shoulder of the patients and telling them to continue their expiration until the hand is lifted, can help. Alternatively, a time cue, such as asking them to continue their effort for "another two seconds" (or some other arbitrarily short and achievable duration) is used, once they have almost reached a plateau.

- FVC specific;

- "Please start with normal breathing. After a few breaths, I will ask you to take as big a breath in as possible to fill your lungs."

- Say, "I want you to breath in as deeeeeeep as possible." Then say, "Deeper."

- Yell, clap your hands, or click your fingers near the patient's ear so as to startle the patient into delivering his or her fastest possible peak flow. And say, "blast it out as hard and as fast as you can"

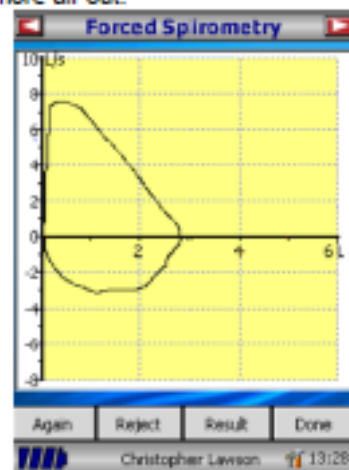
- Tell the patient quietly to "keep going, I can see you're still getting more air out." until a plateau is reached on the volume-time spirogram.

Step 6) Processing of the measurement outcomes

After performing the test you can select different options on the device:

- Again, if the previous maneuver was abnormal
- and you want to perform a new maneuver.
- Reject, if the performed maneuver is not within the range of 5% or the machine gives you the feedback that the test wasn't performed correctly.
- Result, if you want to see the results of the maneuvers performed so far.
- Done, if three sufficient maneuvers have been performed.

Standard Operations Manual For Outcome Measures
ENCALS SOP Version 1.0 May 2016



Other options:

- Select 'done' if the patient performed 3 correct maneuvers (the machine will select automatically the best performed maneuver).
- Select 'print' to print the results of the maneuvers.
- Select 'save' to save the results.

Additional Guidelines

Perform the Vital Capacity test at the beginning of each study visit to avoid fatigue from other testing.

Research(ers) (Nurses) often say, "Okay, take a deep breath and blow out fast. . . *Blow, blow, blow, blow, keep going, keep going, keep going, keep going.*" Emphasis should be on the first phase of the spirometry maneuver (maximum inhalation). This can obtain much larger vital capacities [4].

Facial expressions and body language are much more important than telling the patient what to do. If you recite all of the steps of the procedure (like flight attendants do before each take-off), by the time you have finished, the patient will probably have forgotten the first step, which is the most important. Showing enthusiasm, being a cheerleader, using body language, and observing the patient's body language are very important in order to obtain good spirometry results.[3, 4]

It is crucial that everyone in a multicenter study is using the same predicted values and making racial adjustments the same way and every time.

*The following factors are recommended when using ECCS normal values[8]:

Hong Kong Chinese	100%
Japanese American	89%
Polynesians	90%
North Indians and Pakistanis	90%
South Indians and those of African descent	87%

Care and cleaning of device

- Don't touch the screen with fingers; use only the stylus provided with the device.
- Don't direct the transducer holder towards a strong light source whilst operating the spirometer.
- Clean the transducer on a regular base with Perasafe. Alcohol and chloride solutions should be avoided

SNIP TESTING

Clarification of used terms:

SNIP: The SNIP is measured from functional residual capacity (FRC) in the sitting position using a catheter inserted through a plug occluding one nostril during 10 maximal sniffs through the contralateral nostril. For each test, the largest pressure measured in cm H₂O is taken into account. The SNIP correlates well with invasive and non-volitional tests of diaphragmatic strength but also with the function of the sternocleidomastoid muscle.[2, 5, 9]

Step 1) Calibration

The calibration is factory set and should remain stable indefinitely.

Step 2) Explaining the test

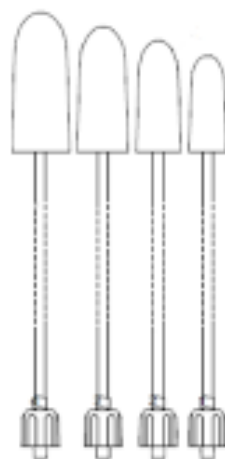
An example of an instruction: Your breathing capacity will be tested using the sniff nasal inspiratory pressure test (SNIP). The SNIP measures the amount of air you can inhale (via your nose) following a sharp short sniff, a total sniff duration of less than 0.5 second[9]. First I will select a popper nasal probe. If the nasal probe fits properly I will ask you to Sniff as hard as you can. This test will be done 10 times to ensure that we measured your best attempt.

The patient could be distracted by people who are around him while performing the VC test. Before you start the measurement, agree with the patient if he wants to perform the test alone so that he can't be distracted by people around him.

Make sure the subject has a complete understanding of the test.

Step 3) Asking for patient's information

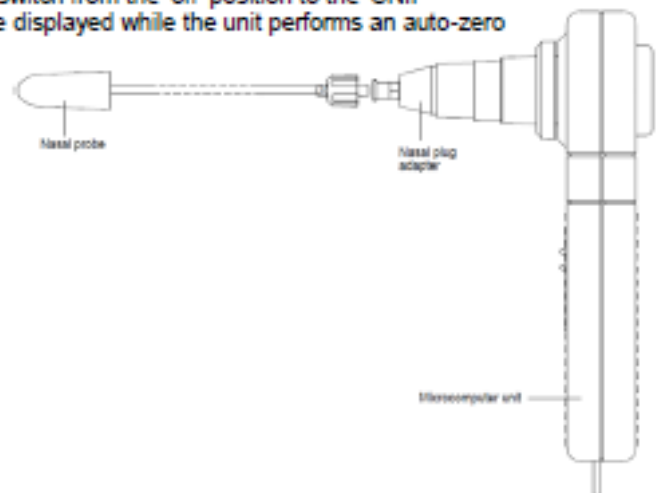
Ask the patient whether he/she has had any type of nasal surgery, is currently experiencing any nasal congestion, or if he/she has a deviated nasal septum (these items could possibly confound results). If the patient's response is positive to one of the items, this should be recorded as such.



Page 6 of 9

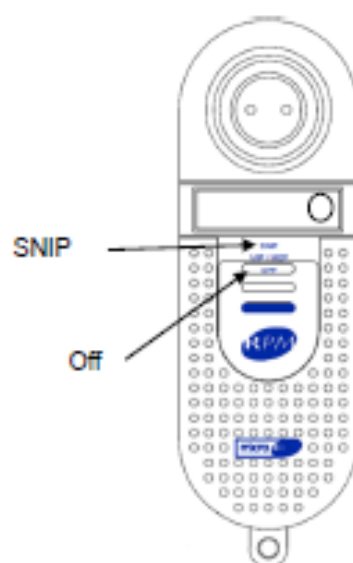
Step 4) Preparing the test

- **Select size:** The correct size (1-4) can be ascertained by fitting a Nasal Probe to the unit, then firmly inserting the Nasal Probe into a nostril.
- **Select nostril:** Select the nostril that seems most appropriate to obtain complete sealing of the nostril.
- **Apply the nasal probe to the selected nostril:** Check if the patient is able to in- and exhale through the nasal probe, by asking him/her to close the other nostril with a finger. Adjust if needed.
- **Attach the nasal probe to the device**
- Turn the device on by sliding the switch from the 'off' position to the 'SNIP' position (rotating segments will be displayed while the unit performs an auto-zero function).



Step 5) Performing the test

- Instruct the patient to sit up straight with legs next to each other.
- In the nasal probe.
- After some tidal breathing, instruct the patient to inhale with as much effort as possible by saying 'Sniff as hard as you can through the free nostril with your mouth closed'.
- Note that the other nostril should NOT be occluded while performing the test.
- The total sniff duration is less than 0.5 second.
- The device will display the peak SNIP in cm H₂O.
- Write down the measurement outcomes.
- Reset the device by sliding the switch from the SNIP position to the 'off' position and back to the SNIP position again.
- Make sure there are at least 30 seconds between each test.



Additional Guidelines

Perform the Vital Capacity testing at the beginning of each study visit to avoid fatigue from other testing.

Care and cleaning of device

The respiratory pressure meter requires no routine maintenance or servicing and is protected from contamination by the bacterial filter supplied. However, the nasal probes may be immersed in cold sterilizing solutions such as alcohol or chloride.

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Appendix 2: Amyotrophic Lateral Sclerosis Functional Rating Scale Revised (ALSFRS-R)

ALS Functional Rating Scale Revised (ALS-FRS-R)

Date:.....Name patient:.....Date of Birth:.....

Patient's number.....Right-/left-handed

Item 1: SPEECH

- 4 ☐ Normal speech process
- 3 ☐ Detectable speech disturbance
- 2 ☐ Intelligible with repeating
- 1 ☐ Speech combined with non-vocal communication
- 0 ☐ Loss of useful speech

Item 2: SALIVATION

- 4 ☐ Normal
- 3 ☐ Slight but definite excess of saliva in mouth; may have nighttime drooling
- 2 ☐ Moderately excessive saliva; may have minimal drooling (during the day)
- 1 ☐ Marked excess of saliva with some drooling
- 0 ☐ Marked drooling; requires constant tissue or handkerchief

Item 3: SWALLOWING

- 4 ☐ Normal eating habits
- 3 ☐ Early eating problems – occasional choking
- 2 ☐ Dietary consistency changes
- 1 ☐ Needs supplement tube feeding
- 0 ☐ NPO (exclusively parenteral or enteral feeding)

Item 4: HANDWRITING

- 4 ☐ Normal
- 3 ☐ Slow or sloppy: all words are legible
- 2 ☐ Not all words are legible
- 1 ☐ Able to grip pen, but unable to write
- 0 ☐ Unable to grip pen

Item 5a: CUTTING FOOD AND HANDLING UTENSILS

Patients without gastrostomy → Use 5b if >50% is through g-tube

- 4 ☐ Normal
- 3 ☐ Somewhat slow and clumsy, but no help needed
- 2 ☐ Can cut most foods (>50%), although slow and clumsy; some help needed
- 1 ☐ Food must be cut by someone, but can still feed slowly
- 0 ☐ Needs to be fed

Item 5b: CUTTING FOOD AND HANDLING UTENSILS

Patients with gastrostomy → 5b option is used if the patient has a gastrostomy and only if it is the primary method (more than 50%) of eating .

- 4 ☐ Normal
- 3 ☐ Clumsy, but able to perform all manipulations independently
- 2 ☐ Some help needed with closures and fasteners
- 1 ☐ Provides minimal assistance to caregiver
- 0 ☐ Unable to perform any aspect of task

Item 6: DRESSING AND HYGIENE

- 4 ☐ Normal function
- 3 ☐ Independent and complete self-care with effort or decreased efficiency
- 2 ☐ Intermittent assistance or substitute methods
- 1 ☐ Needs attendant for self-care
- 0 ☐ Total dependence

Item 7: TURNING IN BED AND ADJUSTING BED CLOTHES

- 4 ☐ Normal function
- 3 ☐ Somewhat slow and clumsy, but no help needed
- 2 ☐ Can turn alone, or adjust sheets, but with great difficulty
- 1 ☐ Can initiate, but not turn or adjust sheets alone
- 0 ☐ Helpless

Item 8: WALKING

- 4 ☐ Normal
- 3 ☐ Early ambulation difficulties
- 2 ☐ Walks with assistance
- 1 ☐ Non-ambulatory functional movement
- 0 ☐ No purposeful leg movement

Item 9: CLIMBING STAIRS

- 4 ☐ Normal
- 3 ☐ Slow
- 2 ☐ Mild unsteadiness or fatigue
- 1 ☐ Needs assistance
- 0 ☐ Cannot do

Item 10: DYSPNEA

- 4 ☐ None
- 3 ☐ Occurs when walking
- 2 ☐ Occurs with one or more of the following: eating, bathing, dressing (ADL)
- 1 ☐ Occurs at rest: difficulty breathing when either sitting or lying
- 0 ☐ Significant difficulty: considering using mechanical respiratory support

Item 11: ORTHOPNEA

- 4 ☐ None
- 3 ☐ Some difficulty sleeping at night due to shortness of breath, does not routinely use more than two pillows
- 2 ☐ Needs extra pillows in order to sleep (more than two)
- 1 ☐ Can only sleep sitting up
- 0 ☐ Unable to sleep without mechanical assistance

Item 12: RESPIRATORY INSUFFICIENCY

- 4 ☐ None
- 3 ☐ Intermittent use of BiPAP
- 2 ☐ Continuous use of BiPAP during the night
- 1 ☐ Continuous use of BiPAP during day & night
- 0 ☐ Invasive mechanical ventilation by intubation or tracheostomy

Interviewer's name.....

Appendix 3: Ethics Application Form

STANDARD APPLICATION FORM

For the Ethical Review of
Health-Related Research Studies, which are not Clinical Trials of Medicinal
Products For Human Use
as defined in S.I. 190/2004

DO NOT COMPLETE THIS APPLICATION FORM

IF YOUR STUDY IS A CLINICAL TRIAL OF A MEDICINAL PRODUCT

Title of Study: Mechanical Insufflation Exsufflation (M-IE) and Lung Volume
Recruitment (LVR) in the Amyotrophic Lateral Sclerosis (ALS)/ Motor Neurone
Disease (MND) population. The prescription process explored.

Application Version No: 1

Application Date: 9th June 2015

For Official Use Only – Date Stamp of Receipt by REC:

TABLE OF CONTENTS MANDATORY /OPTIONAL

SECTION A GENERAL INFORMATION MANDATORY*

SECTION B STUDY DESCRIPTORS MANDATORY*

SECTION C STUDY PARTICIPANTS MANDATORY*

SECTION D RESEARCH PROCEDURES MANDATORY*

SECTION E DATA PROTECTION MANDATORY*

SECTION F HUMAN BIOLOGICAL MATERIAL (OPTIONAL)

SECTION G RADIATION (OPTIONAL)

SECTION H MEDICAL DEVICES (OPTIONAL)

SECTION I MEDICINAL PRODUCTS / COSMETICS / FOOD AND
FOODSTUFFS (OPTIONAL)

SECTION J INDEMNITY AND INSURANCE MANDATORY*

SECTION K COST AND RESOURCE IMPLICATIONS, FUNDING AND
PAYMENTS MANDATORY*

SECTION L ADDITIONAL ETHICAL ISSUES (OPTIONAL)

This Application Form is divided into Sections.

*Sections A, B, C, D, E, J and K are **Mandatory**.

(Sections F, G, H, I and L are optional. Please delete Sections F, G, H, I and L if these sections do not apply to the application being submitted for review.)

IMPORTANT NOTE: Please refer to **Section I** within the form before any attempt to complete the Standard Application Form. **Section I** is designed to assist applicants in ascertaining if their research study is in fact a clinical trial of a medicinal product.

IMPORTANT NOTE: This application form permits the applicant to delete individual questions within each section depending on their response to the preceding questions. Please respond to each question carefully and refer to the accompanying *Guidance Manual* for more in-depth advice prior to deleting any question.

**PLEASE ENSURE TO REFER TO THE ACCOMPANYING GUIDANCE MANUAL
WHEN COMPLETING THIS APPLICATION FORM.**

SECTION A GENERAL INFORMATION

SECTION A GENERAL INFORMATION

SECTION A IS MANDATORY

A1 Title of the Research Study:

Mechanical Insufflation Exsufflation (M-IE) and Lung Volume Recruitment (LVR) in the ALS/MND population. A prospective analysis of the prescription process and participant outcomes.

A2 (a) Is this a multi-site study? No

If you chose 'yes' please delete questions A2 (e) and (f), If you chose 'no' please delete Questions A2 (b) (c) and (d)

A2 (e) If no, please name the principal investigator with overall responsibility for the conduct of this single-site study.

Name: Rachel McConnell

Position: Physiotherapist MISC

Organisation: Beaumont Hospital

Address for Correspondence: Physiotherapy Department, Beaumont Hospital,
Dublin 9

Tel (work): 8528710 **Tel (mob.):** 086 3188 722 **E-mail:**
rachelmcconnell@rcsi.ie

Tel: 8964497 **E-mail:** orla@hardiman.net

A2 (f) For single-site studies, please name the only site where this study will take place.

Beaumont Hospital

A4. Lead contact person who is to receive correspondence in relation to this application or be contacted with queries about this application.

Name: Rachel McConnell

Position: Physiotherapist

Organisation: Beaumont Hospital

Address for Correspondence: Physiotherapy Department, Beaumont Hospital,
Dublin 9

Tel (work): 8528710 **Tel (mob.):** 086 3188 722 **E-mail:**
rachelmcconnell@rcsi.ie

A5 (a) Is this study being undertaken as part of an academic qualification?
Yes

If answer is No, please delete remaining questions in Section A

A5 (b) If yes, please complete the following:

Student Name(s): Rachel McConnell

Academic Course: Masters by Research

Academic Institution: Royal College of Surgeons Ireland (RCSI)

A5 (c) Academic Supervisor(s):

Title: Professor **Name:** Orla Hardiman

Qualification: BSc MB BCh BAO MD FRCPI FAAN

Position: Clinical Professor Consultant Neurologist

Dept: Neurology

Organisation: Beaumont Hospital

Address: Beaumont Road, Dublin 9

Tel: 8964497 **E-mail:** orla@hardiman.net

Title: Dr. **Name:** Deirdre Murray

Qualification: BSc, PhD

Position: Clinical Specialist Physiotherapist

Dept: Physiotherapy

Organisation: Beaumont Hospital

Address: Beaumont Road, Dublin 9

Tel: 8092956 **E-mail:** deirdremurray@beaumont.ie

Title: Dr. **Name:** Dara Meldrum

Qualification: BSc, MSc, PhD, MISCP

Position: Senior Lecturer

Dept: Physiotherapy

Organisation: RCSI

Address: 123 St. Stephen's Green, Dublin 2, Ireland

Tel: 4022368 **E-mail:** dmeldrum@rcsi.ie

Clinical Co Investigator:

Title: Ms. **Name:** Roisin Vance

Qualification: BSc, MSc

Position: Senior Physiotherapist

Dept: Physiotherapy

Organisation: Beaumont Hospital

Address: Beaumont Road, Dublin 9

Tel: 8092526 **E-mail:** roisinmoloney@beaumont.ie

SECTION B STUDY DESCRIPTORS

SECTION B STUDY DESCRIPTORS

SECTION B IS MANDATORY

B1. What is the anticipated start date of this study?

August 2015

B2. What is the anticipated duration of this study?

This study will be carried over three years. For the purpose of Rachel McConnell's masters, an initial one year analysis will be performed for submission of her thesis

B3. Please provide a brief lay (plain English) description of the study. Please ensure the language used in your answer is at a level suitable for use in a research participant information leaflet.

People with Motor Neurone Disease can have a weak cough and this makes it difficult to clear phlegm. Physiotherapists regularly use two devices that can make a cough stronger. The first piece of equipment is a Mechanical Insufflator Exsufflator (sometimes called a cough assistor). This machine blows air into the patient's lungs to give deeper breaths and then it sucks the air out to make a cough stronger. The second piece of equipment is called Lung Volume Recruitment or also called breath stacking. A breathing circuit (a balloon like bag and a face mask) is used to give deep breaths. Both pieces of equipment have been shown to make coughing stronger in people whose cough has become weak such as in Motor Neurone Disease.

There are no guidelines to help physiotherapists to decide when devices should be given to patients with Motor Neurone Disease. This study will look at the patients who are given a device and why they were given it. It will also investigate the differences between those who get a device with those who do not get a device. This study will also look at the effects the devices have on how the lungs work after the two devices are started. This study will also survey the participants and carers experience of the using the devices.

To do this study all patients that come to the Beaumont Hospital Motor Neurone Disease clinic from August 2015 until August 2018 who are interested will be invited to take part. The patients will have their regular assessments and treatments from the multidisciplinary team. This study will document who gets a device, when and why and compare them to those who do not. Participants' information will be gathered at each clinic visit.

If a cough assistor or breath stacking is given to a participant, a questionnaire will be given to them the next time they come to clinic. This questionnaire will look at participants' and carer's experiences and attitudes towards using the devices.

The information collected will analyse why participants got a device when they did. This study will also try to investigate how the muscles that move the lungs work after the two devices are started and if people like or dislike using the devices.

At the moment the practice of prescribing cough assistors and breath stacking is not understood in enough detail. This study aims to improve the care of people with Motor Neurone Disease. It is hoped that doctors and physiotherapists will have a better understanding of when to give a device that can make a cough stronger and what impact these devices are having on patients function and on the lung muscles.

B4. Provide brief information on the study background.

ALS/MND is a fatal neurodegenerative disease of the human motor system involving progressive muscle weakness of voluntary muscles. Respiratory insufficiency is the primary source of mortality and morbidity in ALS/MND (Howard et al. 2002). An effective cough requires sufficient inspiratory muscle strength to ensure adequate inhalation volumes, expiratory muscle strength to generate high thoracoabdominal pressures and upper airway muscle coordination for glottis opening and closing. In ALS/MND an ineffective cough can be attributed to deficiencies in all of these factors.

Two cough augmentation techniques commonly used for airway clearance management in the ALS/MND population are M-IE and LVR. These are M-IE, a device that uses positive and negative pressures to achieve maximum insufflation capacity and increase cough strength and LVR, a technique that also achieves maximum insufflation capacity by stacking breaths and increases cough strength. A resuscitator bag is fitted with a one way valve and a mask or mouth piece. LVR and M-IE are considered to improve the compliance and chest wall range of motion by increasing lung volumes. Increased lung volumes recruit collapsed lung segments,

micro atelectasis is reversed and improves endomural flow (Kang 2006; Kang and Bach 2009; Kang 2005).

Both M-IE and LVR cough augmentation techniques have been assessed in the ALS/MND population. In a randomised cross over control study Senent et al. (2011) assessed the Peak Cough Flow and the subjective perception of seven cough augmentation techniques in 16 stable ALS/MND participants attending an ALS/MND MDT clinic. It found that MIE, followed by LVR combined with an abdominal thrust generated the highest mean Peak Cough Flow (PCF). This study highlighted the immediate increase in PCF that can be achieved with manual and mechanical techniques.

Cleary et al. (2013) found that LVR intervention significantly increased PCF for up to 30 minutes following administration.

Irish ALS/MND Physiotherapy Guidelines published in 2014 (O'Callaghan et al. 2014) recommended regular monitoring of respiratory insufficiency (including PCF) by physiotherapists to direct airway clearance for secretion management. The guidelines advise that carers should be educated in the use of a manually assisted cough to assist with airway clearance. The use of M-IE and LVR to achieve maximum insufflation capacity and assist in mobilising secretions to maintain chest wall compliance and lung compliance is also recommended.

Sufficient evidence based practice or optimal criteria for initiating M-IE and LVR are unclear in the ALS/MND population. The Irish ALS/MND Physiotherapy Guidelines respiratory component lack sufficient detail to adequately guide physiotherapists in the management and prescription of cough augmentation devices. Secretion clearance management in ALS/MND may not be appropriately managed as a result.

Further research on M-IE and LVR prescription to guide physiotherapists is warranted. To identify the optimal criteria for initiating M-IE and LVR among the ALS/MND population, the current practices must first be explored. This study will attempt to explore the prescription practices and the characteristics of participants prescribed and not prescribed a cough augmentation device and attempt to categorise trends and relationships among M-IE and LVR users in the Irish MND/ALS population. This study will also examine participant's change in respiratory function and evaluate participant and carer's experiences following the introduction of M-IE and LVR.

B5. List the study aims and objectives.

Aim 1: Examine the characteristics of participants prescribed M-IE and LVR to understand the prescription process

Objective 1(a): Determine the number of participants prescribed M-IE and LVR

Objective 1(b): Evaluate the clinical characteristics of participants prescribed M-IE and LVR at the time of prescription including disease stage, Slow Vital Capacity (SVC), Sniff Nasal Inspiratory Pressure (SNIP), PCF, Amyotrophic Lateral Sclerosis Functional Rating Scale-revised (ALSFRS-r) and respiratory symptoms

Aim 2: Conduct a preliminary analysis of function, respiratory function and outcome following the introduction of M-IE and LVR

Objective 2(a): Determine preliminary trends in the rate of decline of SVC, SNIP, PCF ALSFRS-r following the introduction of M-IE and LVR

Objective 2(b): Determine preliminary trends in the rates of decline of SVC, SNIP, PCF and ALSFRS-r of participants prescribed M-IE and LVR to participants not prescribed M-IE and LVR

Objective 2(c): Prospectively measure chest infection rates and use of antibiotics for chest infections in the recruited cohort

Aim 3: Evaluate participant and carer experience with the use of M-IE and LVR

Objective 3 (a): Assess M-IE and LVR usability, reported adherence and reported effectiveness

B6. List the study endpoints / measurable outcomes (if applicable).

Aim 1: Quantification of respiratory function at time of prescription of M-IE and LVR

Aim 2: Rates of decline of respiratory function, frequency of chest infections and antibiotic use

Aim 3: Quantification of patient experience/adherence with M-IE and LVR

It is expected that the medical and physiotherapy field will have a more in-depth knowledge of the patient characteristics of patients prescribed a M-IE or LVR to prescribe M-IE and LVR to suitable MND/ALS patients. It is also anticipated that this study will develop understanding of the long term outcomes such as participant respiratory function following the introduction of M-IE and LVR.

B7. Provide information on the study design.

This study is a prospective longitudinal study evaluating the prescription process of M-IE and LVR and their effects on, respiratory function in a cohort of ALS/MND patients over 3 years. A questionnaire will be used to evaluate patient and carer experiences with the M-IE and LVR.

B8. Provide information on the study methodology.

Participants with a diagnosis of ALS/MND confirmed by a neurologist according to El Escorial criteria will be considered for inclusion.

Professor Orla Hardiman, Consultant Neurologist and Academic Supervisor and her team of neurology registrars working at the ALS/MND clinic will inform eligible participants of the study at the ALS/MND multidisciplinary team clinic. Patients

interested in participating in the study will be approached by the lead researcher Rachel McConnell

and will be provided with an information leaflet detailing the study design and their role during the study. Patients will be given sufficient time to discuss this information with family members and to make a decision about participating in this study. They will be given a cooling off period of their own choosing after the study has been explained to them and the information sheet given to them.

Following informed consent, participants will be reviewed at each clinic appointment until August 2018, the duration of the study or until death. All patients at the ALS/MND multidisciplinary team clinic are reviewed by the lead researcher Rachel McConnell as per normal clinic routine. Rachel McConnell is a physiotherapist working in a research capacity as an assessor in the ALS/MND multidisciplinary team clinic. Her role in clinic is to assess SNIP, ALSFRS-r, weight, transcutaneous carbon dioxide and monitor for shoulder pain.

All participants will be reviewed by Rachel McConnell for routine assessments and supplementary tests for the purpose of this study. Additional assessments performed by Rachel McConnell for the purpose of this study are SVC, PCF, the frequency of chest infections and the use of antibiotics for chest infections. All assessments completed by Rachel McConnell will be performed at each clinic for the duration of the study (three years) or until death of the participant.

Participants will be reviewed by the neurologists and the multidisciplinary team as per normal clinic practice. All patients attending the ALS/MND multidisciplinary team clinic are reviewed by the neurologist and are referred to the physiotherapist as determined by the assessing neurologist.

The role of the physiotherapist at the ALS/MND clinic is to provide aids and appliances, to prescribe exercise, to manage pain and to manage respiratory symptoms (O'Callaghan et al. 2014). Not all patients at the ALS/MND multidisciplinary team clinic are referred to physiotherapy. Not all patients referred to physiotherapy are assessed for respiratory management. Participants that are referred to physiotherapy will be reviewed by the physiotherapist for general assessment.

Two physiotherapists, Dr. Deirdre Murray (academic supervisor and Clinical Specialist Physiotherapist) and Rosin Vance (co-investigator and Senior Physiotherapist) work in the ALS/MND multidisciplinary team clinic. There will be one physiotherapist working at each ALS/MND multidisciplinary team clinic. The physiotherapist at clinic will assess referred participants routinely in clinic and prescribe M-IE and LVR if required as determined by the physiotherapist's assessment.

If M-IE and LVR are prescribed to participants the assessing physiotherapist will complete a data collection form detailing the participants SNIP, SVC, PCF values and subjective respiratory symptoms.

Participants who receive M-IE and LVR will be asked to complete a questionnaire at the clinic visit following prescription. This questionnaire will be provided and collected by lead researcher Rachel McConnell. This questionnaire will be piloted on the first three participants who receive M-IE or LVR.

Participant's data including SNIP and ALSFRS-r prior to the commencement of the study will be obtained from the ALS/MND clinical database.

The participant's General Practitioner (GP) will be informed of the study. The GP will be contacted in August 2016 and August 2018 for information on the number of chest infections and antibiotic prescriptions the participants received during the study period.

B9. Provide information on the statistical approach to be used in the analysis of your results (if appropriate) / source of any statistical advice.

Answer: Data will be entered into SPSS. SPSS will be used for analysis.

Descriptive statistics will be used to assess participant and carer experience. A multivariate regression analysis will be used to explore the relationship between participant characteristics and prescription of M-IE and LVR. Summary statistics will be calculated for respiratory function at the time of M-IE and LVR prescription. Respiratory function will be measured by SVC, SNIP and PCF.

Dr. Katy Tobin, a member of the Trinity College Dublin MND research team has been consulted. Further statistical assistance will be sought to analyse the data.

B10 (a) Please justify the proposed sample size and provide details of its calculation (including minimum clinically important difference).

Answer: Our estimate size is based on the data required for an adequate regression analysis and the population size attending the Beaumont Hospital ALS/MND multidisciplinary team clinic. Green (1991) suggests that a sample size of $n \geq 50 + 8m$, m is the number of independent variables is adequate for the testing of multiple correlations and $n \geq 104 + m$ for testing individual predictors.

B10 (b) Where sample size calculation is impossible (e.g. it is a pilot study and previous studies cannot be used to provide the required estimates) then please explain why the sample size to be used has been chosen.

Answer: Non applicable

B11. How many research participants are to be recruited in total?

Answer: A minimum of 109.

B12 (a) How many research participants are to be recruited in each study group (where applicable)? Please complete the following table (where applicable).

Non applicable

Name of Study Group:	Name of Study Group:	Name of Study Group:	Name of Study Group:	Name of Study Group:
Answer	Answer	Answer	Answer	Answer

Number of Participants in this Study Group:	Number of Participants in this Study Group:	Number of Participants in this Study Group:	Number of Participants in this Study Group:	Number of Participants in this Study Group:
Answer	Answer	Answer	Answer	Answer

B12 (b) Please provide details on the method of randomisation (where applicable).

Non applicable

B13. How many research participants are to be recruited at each study site (where applicable)? Please complete the following table.

Non applicable, this is a single site study, taking place at Beaumont Hospital only.

Site:	Number of Research Participants at this site:

SECTION C STUDY PARTICIPANTS

PARTICIPANTS

SECTION C IS MANDATORY

C1 PARTICIPANTS – SELECTION AND RECRUITMENT

C1.1 How will the participants in the study be selected?

Participants who are attending the Beaumont Hospital MND multidisciplinary team clinic with a confirmed diagnosis of ALS/MND by a neurologist according to El Escorial criteria will be considered for inclusion.

C1.2 How will the participants in the study be recruited?

Professor Orla Hardiman, Consultant Neurologist and Academic Supervisor and her team of neurology registrars working at the ALS/MND clinic will inform eligible participants of the study at the ALS/MND multidisciplinary team clinic. Patients interested in participating in the study will be approached by the lead researcher Rachel McConnell for informed consent at the ALS/MND multidisciplinary team clinic.

Patients will be provided with an information leaflet detailing the study design and the participant's role during the study. Patients will be given sufficient time to discuss this information with family members and to make a decision about participating in this study. They will be given a cooling off period of their own choosing after the study has been explained to them and the information sheet given to them.

C1.3 What are the inclusion criteria for research participants? (Please justify, where necessary)

- Diagnosis of ALS according to El Escorial criteria

- Willing to undergo study measurements for the study duration
- Provide informed consent

C1.4 What are the exclusion criteria for research participants? (Please justify, where necessary)

Exclusion criteria

- Unable to understand English
- Have a diagnosis of frontal temporal dementia

C1.5 Will any participants recruited to this research study be simultaneously involved in any other research project?

Yes; Beaumont Hospital often participates in Randomised controlled trials in the MND population. There will be two clinical trials commencing later in 2015.

PARTICIPANTS – INFORMED CONSENT

C2.1 (a) Will informed consent be obtained?

C2.1 (b) If no, please justify. You must provide a full and detailed explanation as to why informed consent will not be obtained.

Answer: Non applicable

C2.1 (c) If yes, please outline the consent process in full. (How will consent be obtained, when, by whom and from whom etc.)

Professor Orla Hardiman, Consultant Neurologist and Academic Supervisor and her team of neurology registrars working at the ALS/MND clinic will inform eligible participants of the study at the ALS/MND multidisciplinary team clinic. Patients interested in participating in the study will be approached by the lead researcher Rachel McConnell for informed consent at the ALS/MND multidisciplinary team clinic.

Patients will be provided with an information leaflet detailing the study design and the participant's role during the study. Patients will be given sufficient time to discuss this information with family members and to make a decision about participating in this study. They will be given a cooling off period of their own choosing after the study has been explained to them and the information sheet given to them.

C2.2 (a) Will participants be informed of their right to refuse to participate and their right to withdraw from this research study?

☒ Yes

C2.2 (b) If no, please justify.

Non applicable

C2.3 (a) Will there be a time interval between giving information and seeking consent? ☒ Yes

C2.3 (b) If yes, please elaborate.

Participants will be given an opportunity to read the information leaflet in the Beaumont Hospital MND/ALS multidisciplinary team clinic and consult with family members before they are asked for informed consent. They will be given a cooling

off period of their own choosing after the study has been explained to them and the information sheet given to them.

C2.3 (c) If no, please justify and explain why an instantaneous decision is reasonable having regard to the rights of the prospective research participants and the risks of the study.

Non applicable

C3 ADULT PARTICIPANTS (AGED 18 OR OVER) - CAPACITY

C3.1 (a) Will all adult research participants have the capacity to give informed consent? ☒ Yes

If answer is Yes, please delete remaining questions in Section C3

C4 PARTICIPANTS UNDER THE AGE OF 18

C4.1 (a) Will any research participants be under the age of 18 i.e. Children? No

If answer is No, please delete remaining questions in Section C4

C5 PARTICIPANTS - CHECKLIST

C5.1 Please confirm if persons from any of the following groups will participate in this study. This is a quick checklist to assist research ethics committee members and to identify whether study participants include persons from vulnerable groups and to establish what special arrangements, if any, have been made to deal with issues of consent. It is recognised that not all groups in this listing will automatically be vulnerable or lacking in capacity. Please refer to the HSE's National Consent Policy, particularly Part 3, Section 5.

Committees are particularly interested to know if persons in any of these groups are being targeted for inclusion, as per the inclusion criteria.

(a) Healthy Volunteers No

(b) Patients Yes

- **Unconscious patients No**
- **Current psychiatric in-patients No**
- **Patients in an emergency medical setting No**

(c) Relatives / Carers of patients Yes

(d) Persons in dependent or unequal relationships No

- **Students No**
- **Employees / staff members No**
- **Persons in residential care No**
- **Persons highly dependent on medical care No**

(e) Intellectually impaired persons No

(f) Persons with a life-limiting condition ☒ Yes

(Please refer to guidance manual for definition)

(g) Persons with an acquired brain injury No

C5.2 If yes to any of the above, please comment on the vulnerability of the research participants, and outline the special arrangements in recognition of this vulnerability (if any).

ALS/MND participants are a vulnerable population due to the progressive nature of the disease. All researchers all have experience working with ALS/MND patients in the multidisciplinary team clinic. This study is not intervening with regular treatments received.

C5.3 Please comment on whether women of child-bearing potential, breastfeeding mothers, or pregnant women will be included or excluded in this research study.

Excluded

SECTION D RESEARCH PROCEDURES

SECTION D IS MANDATORY

D1 (a) What activities, procedures or interventions (if any) are research participants asked to undergo or engage in for the purposes of this research study?

Participants will be attending the Beaumont Hospital MND/ALS multidisciplinary team clinic for their routine appointment. All participants will be assessed by a

doctor and possibly referred to the physiotherapist in clinic. Participants will undergo a regular physiotherapy intervention. No additional physiotherapy interventions will be performed for this study.

All participants will be assessed by lead researcher Rachel McConnell for routine assessments including SNIP, ALSFRS-r, transcutaneous carbon dioxide, monitoring for shoulder pain and weight. Additional assessments performed by Rachel McConnell for the purpose of this study are SVC, PCF the frequency of chest infections and the use of anti biotics for chest infections.

If participants are prescribed a M-IE or LVR device they will be asked to complete questionnaire.

D1 (b) What other activities (if any) are taking place for the purposes of this research study e.g. chart review, sample analysis etc?

The lead researcher will have access to participant's medical chart to ascertain information such as date of diagnosis and past medical history. Data such as SNIP and ALSFRS-r prior to August 2015 will be obtained from the ALS/MND clinical database.

D2. Please provide details below of any potential harm that may result from any of the activities, procedures, interventions or other activities listed above.

There is no foreseen potential harm. This is a prospective longitudinal study of routine interventions.

D3. What is the potential benefit that may occur as a result of this study?

Participants will have comprehensive monitoring of respiratory measurements. The overall benefit of this study aims to improve the respiratory physiotherapy care people with ALS/MND receive. It is expected that there will be an increased understanding of the M-IE and LVR prescription and how it impacts patients function, lung function and outcomes.

D4 (a) Will the study involve the withholding of treatment?

D4 (b) Will there be any harms that could result from withholding treatment?

D4 (c) If yes, please elaborate.

D5 (a) How will the health of participants be monitored during the study, and who will be responsible for this?

Participants will be receiving routine physiotherapy treatment at the Beaumont Hospital ALS/MND multidisciplinary team clinic. Participants' health will be monitored at each clinic visit.

D5 (b) How will the health of participants be monitored after the study, and who will be responsible for this?

On completion of the study participant will continue to attend the Beaumont Hospital ALS/MND multidisciplinary team clinic as is normal clinical practice.

D6 (a) Will the interventions provided during the study be available if needed after the termination of the study?

D6 (b) If yes, please state the intervention you are referring to and state who will bear the cost of provision of this intervention?

Non-applicable

D7. Please comment on how individual results will be managed.

Participants will be given a study number unique identifier. This number will be matched to a name stored on a hard copy that will be locked in a cabinet in Beaumont Hospital. Only the researchers involved in the study will have access to this. Data will be inputted into SPSS using a number unique identifier on a computer that complies with data protection. Electronic records will be stored on a secure encrypted memory stick and a password protected Beaumont hospital desktop PC. Hard copy materials will be stored in a locked filing cabinet in the Physiotherapy Department, Beaumont Hospital for seven years following study completion. If a patient would like the results they may ask the researcher. Participants will be asked if they would like to receive a summary of the research findings. If they indicate that they wish to receive a summary of the findings of the research this will be noted by the lead researcher (RMC) and a summary will be forwarded by post.

D8. Please comment on how aggregated study results will be made available.

The study results will be presented at conferences and published in a journal in format as applicable.

D9. Will the research participant's general practitioner be informed that the research participant is taking part in the study (if appropriate)? ☒ Yes

D10. Will the research participant's hospital consultant be informed that the research participant is taking part in the study (if appropriate)? ☒ Yes

SECTION E DATA PROTECTION

SECTION E IS MANDATORY

E1 DATA PROCESSING - CONSENT

E1.1 (a) Will consent be sought for the processing of data?

E1.1 (b) If no, please elaborate.

Non-applicable	TA PROCESSING - GENERAL
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E2.1 Who will have access to the data which is collected?

Lead researcher and supervisors

E2.2 What media of data will be collected?

Paper and electronic

E2.3 (a) Would you class the data collected in this study as anonymous, irrevocably anonymised, pseudonymised, coded or identifiable data?

Coded

E2.3 (b) If 'coded', please confirm who will retain the 'key' to re-identify the data?

Lead researcher

E2.4 Where will data which is collected be stored?

Password protected laptop, with encrypted protected documents in a locked drawer in a room that is accessible by a code

E2.5 Please comment on security measures which have been put in place to ensure the security of collected data.

Laptop will be in a locked drawer in a room that is accessible by a code

E2.6 (a) Will data collected be at any stage leaving the site(s) of origin?

Yes

E2.6 (b) If yes, please elaborate.

Coded data stored on an encrypted memory key may leave Beaumont Hospital for statistical and academic consultation.

E2.7 Where will data analysis take place and who will perform data analysis (if known)?

Beaumont Hospital. The research team will perform the data analysis with the help from a statistician.

E2.8 (a) After data analysis has taken place, will data be destroyed or retained?

Retained and destroyed

E2.8 (b) Please elaborate.

The data will be retained for seven years after analysis and then destroyed

E2.8 (c) If destroyed, how, when and by whom will it be destroyed?

Deleted from the research laptop following Beaumont Hospital's policies for destroying confidential material

E2.8 (d) If retained, for how long, for what purpose, and where will it be retained?

Seven years. For on-going data analysis. Secured laptop in Beaumont Hospital Physiotherapy Department.

E2.9 Please comment on the confidentiality of collected data.

All data will be coded to insure confidentiality. The excel sheet with participant names will be encrypted and this will remain on a secure laptop in the physiotherapy department.

A hard copy with participant's names and unique identifier number will be locked in a cabinet in the physiotherapy department in a room accessible by a code.

E2.10 (a) Will any of the interview data collected consist of audio recordings / video recordings? No

E2.10 (b) If yes, will participants be given the opportunity to review and amend transcripts of the tapes?

Non-applicable

E2.11 (a) Will any of the study data collected consist of photographs/ video recordings? No

E2.11 (b) If yes, please elaborate.

Non-applicable

E3 ACCESS TO HEALTHCARE RECORDS

E3.1 (a) Does the study involve access to healthcare records (hard copy / electronic)? Yes

If answer is No, please delete remaining questions in Section E3

E3.1 (b) If yes, please elaborate.

Medical charts and physiotherapy charts of participants will be accessed. Access to the ALS/MND clinical database will also be obtained.

E3.1 (c) Who will access these healthcare records?

Lead researcher Rachel McConnell

E3.1 (d) Will consent be sought from patients for research team members to access their healthcare records? Yes

If answer is Yes, please delete remaining questions in Section E3

SECTION F HUMAN BIOLOGICAL MATERIAL

F1 BODILY TISSUE / BODILY FLUID SAMPLES - GENERAL

SECTION F BODILY TISSUE / BODILY FLUID SAMPLES - GENE

F1 1 (a) Does this study involve human biological material? No

SECTION G RADIATION

G1 RADIATION – GENERAL

SECTION G RADIATION

G1 RADIATION – GENERAL

G1.1 (a) Does this study/trial involve exposure to radiation? No

SECTION H MEDICAL DEVICES

SECTION H MEDICAL DEVICES

H1 (a) Is the focus of this study/trial to investigate/evaluate a medical device?

No

**SECTION I MEDICINAL PRODUCTS / COSMETICS / FOOD AND
FOODSTUFFS**

I.1 NON-INTERVENTIONAL TRIALS OF MEDICINAL PRODUCTS

**SECTION I MEDICINAL PRODUCTS / COSMETICS / FOOD AND
FOODSTUFFS**

I.1 NON-INTERVENTIONAL TRIALS OF MEDICINAL PRODUCTS

I1.1 (a) Does this study involve a medicinal product? No

If the answer is No, please delete remaining questions in subsection I1

SECTION J INDEMNITY AND INSURANCE

SECTION J INDEMNITY AND INSURANCE

SECTION J IS MANDATORY

J1 Please confirm and provide evidence that appropriate insurance/indemnity is in place for this research study at each site.

The Beaumont Hospital site has employer's liability insurance and public liability insurance (for personal injuries to its employees) and public liability insurance (for personal injury to members of the public) via The State Claims Agency and professional liability insurance (in respect of claims for loss and injury caused by following professional advice etc.) with IPB (Dublin Hospitals' group policy) (Details on file).

J2 Please confirm and provide evidence that appropriate insurance/indemnity is in place for this research study for each investigator.

Beaumont Hospital employees, agents and servants are covered by employer's liability insurance via State Claims Agency and for professional liability insurance with IPB (Dublin Hospitals' group policy) (Details on file).

Dr. Dara Meldrum an employee of RCSI is indemnified for research via MARSH Ireland for combined liability insurance (attached).

J3.1 Please give the name and address of the organisation / or individual legally responsible for this research study?

Beaumont Hospital, Beaumont Road, Beaumont, Dublin 9 and Royal College of Surgeons Ireland, 123 St. Stephen's Green, Dublin 2.

J3.2 Where an organisation is legally responsible, please specify if this organisation is:

A pharmaceutical company ☐ No

A medical device company ☐ No

A university ? Yes RCSI

A registered charity ☐ No

Other ☒ Yes If yes, please specify: Hospital

J3.3 Please confirm and provide evidence of any specific additional insurance / indemnity arrangements which have been put in place, if any, by this organisation / or individual for this research study?

Non applicable

SE

SECTION K COST AND RESOURCE IMPLICATIONS, FUNDING AND PAYMENTS

SECTION K IS MANDATORY

SECTION K COST AND RESOURCE IMPLICATIONS, FUNDING AND PAYMENTS

K1 COST AND RESOURCE IMPLICATIONS

K1.1 Please provide details of all cost / resource implications related to this study (e.g. staff time, office use, telephone / printing costs etc.)

Equipment: €5,200

College fees: €8,000

Dissemination: €2000

Training: €450

Institutional overheads: €1200

K2 FUNDING

K2.1 (a) Is funding in place to conduct this study?

Yes

K2.1 (b) If no, has funding been sought to conduct this study? From where? Please elaborate.

Non applicable

K2.1 (c) If yes, please state the source of funding (industry, grant or other), the name of the funder, the amount of funding and duration of funding.

Source of funding (industry, grant or other):
Voluntary Organisation
Name of Funder:
Research Motor Neurone
Amount of Funding:

€17,160
Duration of Funding
November 2014-Novemembr 2016

K2.1(d) Please provide additional details in relation to management of funds.

Funds are held by Research Motor Neurone. Payment for expenses is applied for retrospectively with evidence of a receipt.

K2.1(e) Is the study funded by a ‘for profit’ organisation?

K2.2 (a) Do any conflicts of interest exist in relation to funding or potential funding?

K2.2 (b) If yes, please elaborate.

Non applicable

K K3 PAYMENTS TO INVESTIGATORS PAYMENTS TO INVESTIGATORS

K3 PAYMENTS TO INVESTIGATORS

PA

K3.1 (a) Will any payments (monetary or otherwise) be made to investigators?

K3.1 (b) If yes, please provide details of payments (including amount).

Non applicable

K4 PAYMENTS TO PARTICIPANTS

RTICIPANTS

K4.1 (a) Will any payments / reimbursements (monetary or otherwise) be made to participants? No

K4.1 (b) If yes, please provide details of payments / reimbursements (including amount).

Non-applicable

SECTION L ADDITIONAL ETHICAL ISSUES

SECTION L ADDITIONAL ETHICAL ISSUES

L1 (a) Does this project raise any additional ethical issues? No

If answer is No, please delete remaining questions in Section L.

PLEASE ENSURE THIS APPLICATION FORM IS FULLY COMPLETED AS INCOMPLETE SUBMISSIONS WILL NOT BE REVIEWED.

Appendix 4: Beaumont Ethical Approval

Ethics (Medical Research) Committee - Beaumont Hospital Notification of ERC/IRB Approval

Principal Investigator: Ms. Rachel McConnell (Physio)

Consultant co-investigator: Prof. Orla Hardiman

REC reference: 15/62


Protocol Title: Mechanical Insufflation Exsufflation (M-IE) and Lung Volume Recruitment (LVR) in the ALS / MND Population

Ethics Committee Meeting Date: 28th May 2015

Final Approval Date: 13th August 2015

From: Ethics (Medical Research) Committee - Beaumont Hospital, Beaumont, Dublin 9

Document and Date	Documents Reviewed Date Reviewed	Approved
Application Form, V2, 24/7/15	13/8/15	Yes
Protocol, V1, 9/6/15	13/8/15	Yes
Patient Information Leaflet, V2, 24/7/15	13/8/15	Yes
Patient Informed Consent Form, V1, 9/6/15	13/8/15	Yes
Patient Questionnaire, V1, 9/6/15	13/8/15	Yes
GP Letter, V1, 9/6/15	13/8/15	Yes
Data Collection Form, V1, 9/6/15	13/8/15	Yes
Cert of Insurance: RCSI, 1/12/14	13/8/15	Noted
CV: D. Murray / R. McConnell	13/8/15	Noted


Dr. Peter Brannagan
ERC/IRB Convenor's Signature
Approval # 1, dated 13th August 2015

Appendix 5: RCSI Ethical Approval

Royal College of Surgeons in Ireland
The Research Ethics Committee
121 St. Stephens Green, Dublin 2, Ireland.
Tel: +353 1 4022205 Email: recadmin@rcsi.ie

Dr David Smith, Acting Chair
Dr Niamh Clarke, Convenor

5th October 2015

Ms Rachel McConnell,
Physiotherapy Department,
Beaumont Hospital
Dublin 9



Ethics Reference No:	REC 1150
Project Title:	Mechanical Insufflation Exsufflation (M-IE) and Lung Volume Recruitment (LVR) in the ALS/MND population. A prospective analysis of the prescription process and participant outcomes.
Researchers Name (lead applicant):	Ms Rachel McConnell (Dept Physiotherapy, Beaumont Hospital)
Principal Investigator on the project (PI):	Professor Orla Hardiman (academic supervisor, Department of Neurology Beaumont Hospital)
Other Individuals Involved:	Ms Roisin Vance and Dr Deirdre Murray (academic supervisor) both department of Physiotherapy, Beaumont Hospital) and Dr. Dara Meldrum (RCSI academic supervisor, School of Physiotherapy, RCSI, 123 St. Stephens Green)

Dear Ms McConnell,
Thank you for your Research Ethics Committee (REC) application. The RCSI HREC accepts the ethical approval granted by Beaumont Hospital REC for the research study (details above) submitted by Ms Rachel McConnell.

This letter provides approval for data collection for the time requested in your research study and for an additional 6 months. This is to allow for any unexpected delays in proceeding with data collection. Therefore this research ethics approval will expire on 5th April 2019.

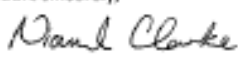
Where data collection is necessary beyond this point, approval for an extension must be sought from the Research Ethics Committee.

This ethical approval is given on the understanding that:

- All personnel listed in the approved application have read, understand and are thoroughly familiar with all aspects of the study.
- Any significant change which occurs in connection with this study and/or which may alter its ethical consideration must be reported immediately to the REC, and an ethical amendment submitted where appropriate.
- Please submit a final report to the REC upon completion of your project.

We wish you all the best with your research.

Yours sincerely,


PP Dr Niamh Clarke (Convenor)
Dr David Smith (Acting Chair)

Appendix 6: Patient Information Leaflet



Patient Information Leaflet



Study title: Mechanical Insufflation Exsufflation (M-IE) and Lung Volume Recruitment (LVR) in ALS/MND: a prospective study of the prescription process and patient outcomes.

Principal investigator's name:	Rachel McConnell
Principal investigator's title:	Physiotherapist
Telephone number of principal investigator:	01-8092526
Consultant co-investigator's name:	Professor Orla Hardiman
Consultant co-investigator's title:	Clinical Professor Neurology Consultant
Academic Supervisor:	Dr. Deirdre Murray
Academic Supervisor title:	Clinical Specialist Physiotherapist
Academic Supervisor name:	Dr. Dara Meldrum
Academic Supervisor title:	Senior Lecturer, School of Physiotherapy, Royal College of Surgeons Ireland
Co-investigator's name:	Roisin Vance
Co-investigator's title:	Senior Physiotherapist

You are being invited to take part in a clinical research study to be carried out at Beaumont Hospital Motor Neurone Disease/Amyotrophic Lateral Sclerosis Multidisciplinary Team Clinic.

Before you decide whether or not you wish to take part, you should read the information provided below carefully and, if you wish, discuss it with your family, friends or GP (doctor). Take time to ask questions – don't feel rushed and don't feel under pressure to make a quick decision.

You should clearly understand the risks and benefits of taking part in this study so that you can make a decision that is right for you. This process is known as 'Informed Consent'.

Version: 1

Date: 9th June 2015

Page 1

You don't have to take part in this study. If you decide not to take part it won't affect your future medical care.

You can change your mind about taking part in the study any time you like. Even if the study has started, you can still opt out. You don't have to give us a reason. If you do opt out, rest assured it won't affect the quality of treatment you get in the future.

Why is this study being done?

You have been asked to take part in this research study that looks at two devices that can help people with Motor Neurone Disease to cough stronger. Some people with Motor Neurone Disease can have a weak cough and this makes it difficult to clear phlegm. The first device is called "Mechanical Insufflation Exsufflation" or sometimes called a cough assistor. The second device is called "Lung Volume Recruitment" or more simply called breath stacking.

This study will look at who is given a device and why they were given it. It will also explore the differences between the people who do get a device and the people who do not get a device. This study will also try to find out how the muscles that move the lungs work after the two devices are started. Lastly, this study will use a questionnaire to ask the patients and carer's who did get the devices if they liked using them.

Who is organising and funding this study?

This study is being conducted by Rachel McConnell who is a Physiotherapist that works in the Beaumont Hospital Motor Neurone Disease multidisciplinary team clinic. This study is part of Rachel McConnell's masters, an academic qualification she is undertaking with the Royal College of Surgeons Ireland (RCSI). This study is being funded by Research Motor Neurone.

Why am I being asked to take part?

You are being asked to take part in this study because of your diagnosis of Motor Neurone Disease and because you attend the Beaumont Hospital Motor Neurone Disease multidisciplinary team clinic.

How will the study be carried out?

This study will involve taking three breathing tests, answering two questionnaires and asking you if you have had any recent chest infections and if you have used anti-biotics to treat the chest infections. The three breathing tests are called Sniff Nasal Inspiratory Pressure, Peak Cough Flow and Slow Vital Capacity. One breathing test will involve sniffing, another test will look at the strength of your cough and another test will look at how much air you can blow out after you take a deep breath. One breathing test, the Sniff Nasal Inspiratory Pressure test is normally taken at each clinic and the other two tests will be extra for the study.

One questionnaire is normally taken at clinic and this looks at your symptoms. The second questionnaire will ask you a number of questions about the cough assistor and breath stacking

Version: 1

Date: 9th June 2015

Page 2

and how you liked using it. This is an extra questionnaire that you will be asked to complete once and it will take about five minutes to answer.

The lead researcher Rachel McConnell will also contact your GP to answer questions about the number of chest infections if any you were treated for during the time of the study.

Between 110 and 130 people with Motor Neurone Disease will be asked to take part in this study.

What will happen to me if I agree to take part?

You do not have to attend Beaumont Hospital for any extra visits. The study will take place over one year.

If you agree to take part in this study you will be assessed by the lead researcher Rachel McConnell at each clinic visit that you attend. Rachel McConnell will take your three breathing tests and ask you about your symptoms and if you have had a chest infection since your last clinic visit. This will take about 20 minutes. You will be asked to answer the questionnaire about the cough assistor and breath stacking once during the study, only if you were given a piece of equipment.

What other treatments are available to me?

This study does not involve any change to your current treatment plan. You can change your mind about taking part in the study any time you like. Even if the study has started, you can still opt out. You don't have to give us a reason. If you do opt out, rest assured it won't affect the quality of treatment you get in the future.

What are the benefits?

Participants will have the benefit of having a more detailed monitoring of the muscles that work their lungs. However, the overall benefit of this study aims to improve the care people with Motor Neurone Disease get by helping doctors and physiotherapists decide when to give a device that can make a cough stronger.

What are the risks?

There are minimal risks if you take part in this study. You may experience some discomfort or breathlessness when performing the breathing tests. This study is not changing the treatment that you receive in Beaumont Hospital Motor Neurone Disease multidisciplinary team clinic.

Will it cost me anything to take part?

This study will not require you to spend any extra money. This study will take part in the Beaumont Hospital Motor Neurone Disease multidisciplinary team clinic at your normal appointment time.

Is the study confidential?

When you enter the study you will be given a unique number and from then only this number will be used to identify you (on study paper or computer files). The code will be kept on one sheet in a locked cabinet in Beaumont Hospital that only the researchers can access. Your name will not be published and it will not be disclosed to anyone outside the hospital.

As part of this study the researcher will be looking at your medical chart. Other researchers involved in this study including Professor Orla Hardiman, Dr. Dara Meldrum, Dr. Deirdre Murray and Roisin Vance will be looking at your information. The information will be kept securely for seven years and during this time it may be used for research in the future. After this time your information will be destroyed securely.

The results of this study will be published in a medical journal and presented at medical conferences. There will be no way of linking your information to the publications or presentations.

Your GP will be contacted and informed that you are taking part in this study.

Where can I get further information?

If you have any further questions about the study or if you want to opt out of the study, this will not affect the quality of treatment you get in the future.

If you need any further information now or at any time in the future, please contact

Rachel McConnell

Physiotherapist,
Physiotherapy Department,
Beaumont Hospital,
Beaumont Road,
Dublin 9

Tel: 01 809 2526

Dr. Deirdre Murray,

Clinical Specialist Physiotherapist,
Physiotherapy Department,
Beaumont Hospital,
Beaumont Road,
Dublin 9

Tel: 01 8528710

Appendix 7: Patient Informed Consent Form



Patient Informed Consent Form



Title of Study: Mechanical Insufflation Exsufflation (M-IE) and Lung Volume Recruitment (LVR) in ALS/MND: a prospective study of the prescription process and patient outcomes.

<i>I have read and understood the Information Leaflet about this research project. The information has been fully explained to me and I have been able to ask questions, all of which have been answered to my satisfaction.</i>	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<i>I understand that I don't have to take part in this study and that I can opt out at any time. I understand that I don't have to give a reason for opting out and I understand that opting out won't affect my future medical care.</i>	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<i>I am aware of the potential risks of this research study.</i>	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<i>I give permission for researchers to contact my GP regarding chest infection frequency and anti-biotic use. I have been assured that information about me will be kept private and confidential.</i>	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<i>I have been given a copy of the Information Leaflet and this completed consent form for my records.</i>	Yes <input type="checkbox"/>	No <input type="checkbox"/>
Storage and future use of information: <i>I give permission for material/data to be stored for possible future research related to the current study without further consent being required</i>	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Participant Name (Block Capitals): _____

Participant Signature: _____

Date: _____

To be completed by the Principal Investigator or his nominee.

I the undersigned have taken the time to fully explain to the above patient the nature and purpose of this study in a manner that they could understand. I have explained the risks involved as well as the possible benefits. I have invited them to ask questions on any aspect of the study that concerned them.

Name (Block Capitals): _____

Qualifications: _____

Signature: _____

Date: _____

3 copies to be made: 1 for patient, 1 for PI and 1 for practice records (if relevant).

Appendix 8: Amyotrophic Lateral Sclerosis Functional Rating Scale Revised Standard Operating Procedure

Revised ALS Functional Rating Scale (ALSFRS-R)

Standard operating procedure

The ALSFRS-R is a scale designed to assess function at home as rated by the patient. The patient should not be prompted in any way, except as described in the SOP, either by the person administering the scale or by a caregiver. If the scale is administered over the telephone and the patient is unable to respond because of significant bulbar impairment, a caregiver should relay the questions and responses. The only situation in which prompting is permitted is if the patient response is clearly at odds with observation. In that case, the person administering the scale should read out the list of choices.

These notes are designed to help clarify some of the ambiguities that can arise in the administration of this scale. The initial question is stated, but the person administering the questionnaire should explore the patient's response further if needed.

As a general rule, "help" means help from a person or a device or appliance. For example a handrail, ankle foot orthosis or walking stick would count as help. The only exception is question 5a where modification of cutlery to make the handles larger is allowed (but counts as slow or clumsy).

ALSFRS-R Questions

1. SPEECH

Ask "How is your speech?" Normal speech means it is exactly the same as before the onset of ALS symptoms. "Detectable speech disturbance" refers to any change noticed either by the patient or the carer not attributable to an obvious cause such as new dentures. "Intelligible with repeating" means that >25% of the time, repeating is necessary for comprehension. "Speech combined with non-vocal communication" means that writing, use of speech synthesizers or similar methods are needed to supplement speech.

- 4 Normal speech process
- 3 Detectable speech disturbance
- 2 Intelligible with repeating
- 1 Speech combined with non-vocal communication
- 0 Loss of useful speech

2. SALIVATION

Ask "How is your saliva?" and score as reported regardless of medication use. Some people have a dry mouth and may report that; if there is no excess saliva, score as normal. "Slight saliva" with or without night time drooling, means that there is an excess, but there is usually no need to mop up the saliva with a tissue. "Moderately excessive saliva" means that a tissue needs to be used, but <25% of the time. "Marked excess of saliva" means that there is likely to be drooling and a tissue is often, but not always used. "Marked drooling" requires a constant use of tissue or handkerchief, or suction.

- 4 Normal
- 3 Slight but definite excess of saliva in mouth; may have night time drooling
- 2 Moderately excessive saliva; may have minimal drooling
- 1 Marked excess of saliva with some drooling
- 0 Marked drooling

3. SWALLOWING

Ask "How is your swallowing?" Normal means that there is no change from before symptom onset; they should be able to eat any food in typical mouthful sizes or drink liquid without difficulty. "Early eating problems" means that occasionally food will stick, or cause coughing or choking. Food may need to be cut up small, but is not mashed or liquidized. "Dietary consistency changes" means that food needs to be mashed or liquidized, drinks may need thickener, or some foods such as steak, dry biscuits or cornflakes are avoided in favour of yoghurts, casseroles or porridge. "Needs supplemental tube feeding" means that oral intake of food is so difficult that significant weight loss (>10%) has occurred and gastrostomy is required to supplement caloric intake *regardless of whether one is fitted or not*. NPO is exclusively parental or enteral feeding.

- 4 Normal eating habits
- 3 Early eating problems – occasional choking
- 2 Dietary consistency changes
- 1 Needs supplemental tube feeding
- 0 NPO

4. HANDWRITING

Ask "Are you able to hold a pen?" If the answer is "Yes" then ask "How is your writing?" and explore whether words are legible. Only score the dominant hand and only score for use of a standard pen of normal size. "Slow or sloppy, all words are legible" means that using a normal pen there is a change in writing. The person may need to use large pen grips or other writing aids. "Not all words are legible" means that some words cannot be read but others can. Ignore ability to write name or sign legibly. If the patient can only write their name or sign legibly, but other writing is illegible, score as 1. If the patient has not written other words except their name or signature recently and therefore cannot answer the question further, score as 1.

- 4 Normal
- 3 Slow or sloppy: all words are legible
- 2 Not all words are legible
- 1 No words are legible, but can still grip pen
- 0 Unable to grip pen

5a. CUTTING FOOD AND HANDLING UTENSILS: Patients without gastrostomy

If someone has a gastrostomy but it is not the primary method of caloric intake, treat as "without gastrostomy". Ask "How are you with cutting food or handling cutlery?" Normal means that there is no change compared with before symptom onset, and there has been no change in the type of utensil used (for example chopsticks to knife and fork, or tendency to use a spoon now). "Somewhat slow and clumsy, but no help needed" means that there is some difficulty either cutting food or holding utensils, but the patient is able to do this independently. Use of large handled cutlery to achieve the task counts as slow and clumsy. "Can cut most foods although slow and clumsy; some help needed" means that occasionally assistance is needed, but the patient is independent for the task otherwise. "Food must be cut by someone but can still feed slowly" means that assistance is required at least half the time for cutting but not for feeding. For example, if food must be cut but the patient can feed themselves otherwise, score 1. "Needs to be fed" means that assistance is needed for any aspect of the task to be achieved. If someone decides not to cut food or feed themselves but might otherwise be able to, then score 0.

- 4 Normal
- 3 Somewhat slow and clumsy, but no help needed
- 2 Can cut most foods (> 50%), although slow and clumsy; some help needed
- 1 Food must be cut by someone, but can still feed slowly
- 0 Needs to be fed

5b. CUTTING FOOD AND HANDLING UTENSILS: Patients with gastrostomy

If someone has a gastrostomy and it is the primary method of caloric intake, treat as "with gastrostomy". Ask "How are you with handling the gastrostomy fastenings and fixtures?" Normal means that there is no difficulty at all with any manipulations.

- 4 Normal
- 3 Clumsy, but able to perform all manipulations independently
- 2 Some help needed with closures and fasteners
- 1 Provides minimal assistance to caregiver
- 0 Unable to perform any aspect of task

6. DRESSING AND HYGIENE

Ask "How are you with dressing or washing?" Normal means there is no change compared with before symptom onset. "Independent but with effort or decreased efficiency" means the person is slower than before but remains independent, and does not use any assistance from either another person or a device such as a button hook. "Intermittent assistance or substitute methods" means that some help is needed either from a caregiver or by use of devices such as button hooks or self-tying laces, but the patient is otherwise independent. If the patient has changed the clothing they normally wear such as having zipped clothing instead of buttons, score as substitute method. "Needs attendant for self-care" means that all aspects of the task require assistance, but the patient is able to assist the caregiver for much of it. "Total dependence" means that the patient is completely unable to carry out any aspect of the task and cannot significantly help the caregiver. If someone decides not to dress or bathe themselves but would otherwise be able to, score 0.

- 4 Normal function**
- 3 Independent; Can complete self-care with effort or decreased efficiency**
- 2 Intermittent assistance or substitute methods**
- 1 Needs attendant for self-care**
- 0 Total dependence**

7. TURNING IN BED AND ADJUSTING BED CLOTHES

Ask "Can you turn in bed and adjust the bed clothes?" If there is difficulty with either or both, then rate 3. If there is great difficulty, as long as the patient can perform at least one of the activities independently, rate 2. "Can initiate, but not turn or adjust sheets alone" means that the process of turning is begun in some way by the person, but someone else needs to provide the assistance required to complete the task. If one task can be completed independently but not the other, score as 2. If both require assistance to complete, score 1. "Helpless" means that initiation of turning is impossible.

- 4 Normal function**
- 3 Somewhat slow and clumsy, but no help needed**
- 2 Can turn alone, or adjust sheets, but with great difficulty**
- 1 Can initiate, but not turn or adjust sheets alone**
- 0 Helpless**

8. WALKING

Ask "How is your walking?" Normal means that there is no change from walking ability before symptom onset. "Early ambulation difficulties" means that there is some difficulty walking which might include slowing, tripping or imbalance, but no assistance is routinely needed either in the form of help from someone else, or by the use of an ankle-foot orthosis, a walking stick, or frame. If assistance from a physical aid or caregiver is needed, score 2. If the patient can help with transfers by weight bearing, score 1.

- 4 Normal**
- 3 Early ambulation difficulties**
- 2 Walks with assistance**
- 1 Non-ambulatory functional movement only**
- 0 No purposeful leg movement**

9. CLIMBING STAIRS

Ask "Are you able to climb stairs?" Only rate ability for walking up stairs, not down. Normal means that there is no change from the situation before symptom onset. Slow means there is some slowing but the patient does not rest between steps or feel unsteady. If they do need to rest or feel unsteady, score 2. "Needs assistance" means use of a handrail or help from a caregiver is required to climb stairs. If someone decides they do not want to climb stairs but would seem otherwise able, score 0.

- 4 Normal
- 3 Slow
- 2 Mild unsteadiness or fatigue
- 1 Needs assistance
- 0 Cannot do

10. DYSPNOEA

Ask "Do you become breathless?" Score the patient regardless of the apparent cause of breathlessness. If someone is using non-invasive ventilation at night or in the day for ALS, score 0. "Walking" means walking at a comfortable speed on the flat.

- 4 None
- 3 Occurs when walking
- 2 Occurs with one or more of the following: eating, bathing, dressing
- 1 Occurs at rest: difficulty breathing when either sitting or lying
- 0 Significant difficulty: considering using mechanical respiratory support

11. ORTHOPNOEA

Ask "Can you sleep lying down flat or do you need to be propped up?" Score based on difficulty regardless of the apparent underlying cause (so for example, needing to sleep sitting up because of excessive saliva scores 1). Treat a hospital style bed in which the back can be raised independently as if pillows were in place of the raised section. If there is difficulty falling asleep or if the patient wakes because of breathlessness but they do not use more than two pillows, score 3. If more than two pillows are needed, or the back is raised up to at least 45 degrees, score 2. If the patient sleeps sitting up in bed or in a chair, score 1. If non-invasive ventilation is used most or all of the night, score 0. If NIV is used for an hour or so only, score as if not used.

- 4 None
- 3 Some difficulty sleeping at night due to shortness of breath, does not routinely use more than two pillows
- 2 Needs extra pillows in order to sleep (more than two)
- 1 Can only sleep sitting up
- 0 Unable to sleep without mechanical assistance

12. RESPIRATORY INSUFFICIENCY

Ask "Do you use non-invasive ventilation?" Regard BiPAP as any form of non-invasive ventilation.

- 4 None
- 3 Intermittent use of BiPAP
- 2 Continuous use of BiPAP during the night
- 1 Continuous use of BiPAP during day & night
- 0 Invasive mechanical ventilation by intubation or tracheostomy

Appendix 9: General Practitioner Letter



Study title: Mechanical Insufflation Exsufflation (M-IE) and Lung Volume Recruitment (LVR) in ALS/MND: a prospective study of the prescription process and patient outcomes.

Date

I am conducting a study to investigate the prescription practices and patient outcomes of patients with Motor Neurone Disease who use cough assist machines and breaths stacking. The title of the study is **“Mechanical Insufflation Exsufflation (M-IE) and Lung Volume Recruitment (LVR) in Amyotrophic Lateral Sclerosis/ Motor Neurone Disease (ALS/MND): a prospective study of the prescription process and patient outcomes”**

Xxx has been recruited to the study. The details are as follows: S/he will attend his routine ALS/MND multidisciplinary team clinic in Beaumont Hospital and receive his routine assessments and physiotherapy treatment. In addition to his routine assessments that include Sniff Nasal Inspiratory Pressure (SNIP) and Amyotrophic Lateral Sclerosis Functional Rating Scale-revised (ALSFERS-r), two additional respiratory measurements, Peak Cough Flow (PCF) and Slow Vital Capacity (SVC) will be assessed. At each clinic visit s/he will be asked if s/he has had a chest infection and if s/he has received antibiotics for treatment of a chest infection since his last clinic review. A questionnaire will also be provided to complete once over the study if a device was prescribed.

Your patient will be attending the Beaumont Hospital ALS/MND multidisciplinary team clinic for assessment.

Ethical approval has been granted by Beaumont Hospital Medical Ethics Committee (REC 1150).

Xxx has given consent for me to contact you to gather further detail of his chest infection frequency and anti-biotic treatment. I will be in contact at a future date for this information.

Version: 1

Date: 9th June 2015

Page:1

If you have any queries please do not hesitate to contact me. I can be contacted at 8528710

Yours sincerely,

Rachel McConnell BSc. MISC

Academic Supervisors

Professor Orla Hardiman, Clinical Professor Neurology Consultant

Dr. Deirdre Murray, Clinical Specialist Physiotherapist, Beaumont Hospital

Dr. Dara Meldrum, Senior Lecturer, School of Physiotherapy, Royal College of Surgeons Ireland

Appendix 10: Physiotherapist Data Collection Form

Physiotherapist Form

ID:

Date:

Device:

PCF:

SNIP:

SVC:

Did the patient have respiratory symptoms?

Yes

☐

No

☐

What respiratory symptoms did the patient have?

Dyspnoea

☐

Productive Cough

☐

Ineffective cough

☐

Audible secretions

☐

Reported secretion retention

☐

Reported inability to clear secretions

☐

Fatigue with coughing

☐

Appendix 11: Questionnaire



Patient Questionnaire



Study title: Mechanical Insufflation Exsufflation (M-IE) and Lung Volume Recruitment (LVR) in ALS/MND: a prospective study of the prescription process and patient outcomes.

This questionnaire is part of a research study called:

Mechanical Insufflation Exsufflation (M-IE) and Lung Volume Recruitment (LVR) in ALS/MND: a prospective study of the prescription process and patient outcomes.

You have been given a cough assist machine or a breath stacking bag.



Cough Assist Machine



Breath Stacking

Please answer the following questions based on your experience using the cough assist machine and the breath stacking bag.

1. What device did you receive/do you have?

Cough Assist Machine

Breath Stacking

Both

2. Did you use it alone or with a family member or carer

Alone

Family member or carer

3. How often were you advised to use the device?

More than 3 times a day	3 times a day	2 times a day	Once a day	1 to 6 times a week	Less than 4 times a month	Not at all
-------------------------------	------------------	------------------	------------	---------------------------	---------------------------------	------------

4. How often did you use the device?

More than 3 times a day	3 times a day	2 times a day	Once a day	1 to 6 times a week	Less than 4 times a month	Not at all
-------------------------------	------------------	------------------	------------	---------------------------	---------------------------------	------------

5. I think the device was easy to use.

Strongly Disagree				Strongly Agree
1	2	3	4	5

6. I think the device was comfortable to use.

Strongly Disagree				Strongly Agree
1	2	3	4	5

7. The device made my cough stronger

Strongly Disagree				Strongly Agree
1	2	3	4	5

8. I was confident using the device.

Strongly Disagree				Strongly Agree
1	2	3	4	5

9. I felt that I knew how to use the device leaving the Motor Neurone Disease clinic.

Strongly Disagree				Strongly Agree
1	2	3	4	5

10. Did you have a chest infection since receiving the piece of equipment?

Yes

☐

No

☐

11. If yes. The device helped my cough during the infection.

Strongly Disagree				Strongly Agree
1	2	3	4	5

12. The device made my speech louder.

Strongly Disagree				Strongly Agree
1	2	3	4	5

13. The device was easy to clean.

Strongly Disagree				Strongly Agree
1	2	3	4	5

Other comments:

Thank you for taking time to complete this questionnaire.

Version: 1

Date: 9th June 2015

Page:4

Rachel McConnell,
Physiotherapist,
Physiotherapy Department,
Beaumont Hospital,
Beaumont Road,
Dublin 9

Tel: 01 809 2526

Version: 1

Date: 9th June 2015

Page:5

Appendix 12: Electrical Engineer's Report

Overview

This technical report presents a description of the hardware and the firmware used in the prototype of the Adherence Device. The device is a datalogger for use with the Breath Stacker apparatus. The device records the date and time that the breath stacker apparatus is used.

The standard breath stacker consists of a compressible vessel (the resuscitator bag) and a facemask. A patient or care assistant holds the facemask against the patient's face. The facemask has a compressible cushion which is placed in direct contact with the patient's face. The primary vessel is compressed, and positive pressure is thus forced towards the patient's trachea. Due to the nature of this procedure, there must be a good seal between the patient's face and the mask.

The adherence device is designed to track the usage of the breath stacker. This is done indirectly via a pressure sensor retro-fitted to the cushion of the facemask. Sufficient pressure inside this cushion indicates that the mask is pressed against a patient's face, and so it can be assumed that the device is in use. Note: neither the pressure of the compressible vessel itself, nor the pressure in the primary area of the facemask is monitored. Only the compressible cushion of the facemask is monitored. Analysis of the collected data can indicate when this device was likely to have been used, and can indicate the times when the mask was likely to have been erroneously compressed.

The prototype device is designed to reside in a low-power/deep sleep mode in order to conserve battery life. When the breath stacker apparatus is moved, the device will wake up. If the breath stacker is used, a timestamp will be recorded. After use, the device will go back into deep sleep once the apparatus is idle for a predetermined amount of time.

The device is designed to reside with a patient for up to three months. After the breath stacker has been returned to the clinician or researcher, the data can be retrieved by via micro SD card.

One single prototype has been designed using a development board. The primary constraints imposed during this design process were size and power. The device has to be physically small and not impede the standard operation of the breath stacker. The power consumption had to be sufficiently low (and the power supply had to be sufficiently high) so that the device can remain alive for up to three months.

This technical report presents a description of the hardware and the firmware of this device. The results obtained from several trials are presented, and the scope of the future work relating to this device is explained.

Bill of materials

Amount required	Functional component	Selected component	Manufacturer	Cost EUR €
1	Development Board	Rocket Scream Mini Ultra 8MHz	Rocket Scream Electronics, Malaysia	9.97
1	Piezoelectric pressure sensor	SSCDANN005PGAA3	Honeywell, USA	37.26
1	Real Time Clock (RTC)	RV8523	Micro Crystal Switzerland IC embedded on module manufactured by Watterott Electronic, Germany	11.90
1	Micro SD card breakout board	MIKROE-429	MikroElektronika, Serbia	16.10
1	Micro SD card	Generic micro SD card	generic/unknown	15.60
2	Tilt switches	RBS040110	OncQue, Taiwan	2.50
1	Non-latching tactile push button switch	Generic non-latching push button switch	generic/unknown	2.50
1	Q1: NPN Darlington pair	MPSA29G BJT	ON Semiconductor, AZ, USA	0.36
1	Q2: NPN	2SC3332 BJT	ON Semiconductor, AZ, USA	0.50
1	Q3: PNP	MPSA56 BJT	ON Semiconductor, AZ, USA	0.36
1	R1: 33k Ω	Generic 33k Ω resistor	generic/unknown	0.09
2	R2 and R5: 10k Ω	Generic 10k Ω resistor	generic/unknown	0.58
1	R3: 1k Ω	Generic 1k Ω resistor	generic/unknown	0.63
1	R4: 33M Ω	Generic 33M Ω resistor	generic/unknown	0.24
2	C1 and C2: 22 μ F 10V	Generic 22 μ F 10V capacitors	generic/unknown	1.35
1	Battery	LS17500CNA (3.6V 3.6Ah)	SAFT, France	9.73
1	Plastic tubing	Generic clear plastic tubing	unknown	0.50

1	Mask Assembly	AMFM2055/001	Armstrong Medical Ltd.	18.00
				Total: 128.17

Prototype dimensions

15.1 Device dimensions (not including facemask)

44mm x 28mm x 15mm (not including battery).

53mm x 43mm x 18mm (including SAFT battery).

15.2 Dimensions of individual components

MIKROE-429 micro SD card breakout board: 26.29mm x 18.54mm

RV8523 RTC Breakout board: 26mm x 26mm

Rocket Scream Mini Ultra 8MHz development board: 18.41 mm x 39.37 mm

SAFT LS17500CNA non-rechargeable Li-SOCl₂ cell: Diameter: 16.85mm.

Length: 50.3mm

Hardware Related Technical Details

16.1 Facemask Assembly (AMFM2055/001)

Considering the small number of devices that were required, the decision was made to try and create a prototype using commercially available modules and components. If the prototype met all the design constraints in terms of size, weight, power, aesthetics and robustness then a small batch could be considerably be easily constructed.

The prototype is retro-fitted to this commercially available facemask assembly. The AMFM2055/001 (Armstrong Medical Ltd., U.K.) was used for this prototype as this facemask assembly is commonly paired with the resuscitator bag to form the breath stacker apparatus. This mask contains a one-way valve and is designed for single patient use.

16.2 Rocket Scream Mini Ultra 8MHz development board

This development board was chosen due to its small size and low current requirements. It has an ATMEGA328P-AU microcontroller on board. The manufacturer of this development board also created a low power library that provides excellent functions for putting the device into an ultra-low power/deep sleep mode. This microcontroller offers all the functionality that the device requires.

The development board operates at 3.3V and the on-board regulator provides 3.3V. As a result, the decision was made to drive the entire device at 3.3V. All modules and peripherals require 3.3V or less to operate.

16.3 Piezoelectric pressure sensor (SSCDANN005PGAA3)

The cushion in the facemask was estimated to reach a maximum pressure of approximately 5 PSI (gage) when highly compressed. As a result, a piezoelectric pressure sensor that could withstand pressures up to approximately 5 PSI was required. There are many brands and form factors of piezoelectric pressure sensors available. For ease of prototyping, inline pin forms were preferred over SMT. Amplified sensors were preferred to save the need to design and build a separate amplification circuit. 3V operation was preferred as the entire device is designed to operate at 3.3V. Low power consumption was important to ensure longevity of the device's battery. Either analogue or digital output was deemed acceptable; however analogue output was preferred for this implementation as other peripherals that would be on the I2C bus.

Honeywell (MN, USA) has a wide variety of sensors and the SSCDANN005PGAA3 was selected for use in this device. This sensor provides an analogue output relating to the pressure sensed in the range of 0 to 5 PSI (gage). The rated over-pressure and burst-pressure levels of this chosen sensor are acceptable considering the expected pressure ranges. This sensor offers a barbed nozzle, however either barbed or barbless appear to be suitable.

In order to mount this to the facemask, a hole was carefully drilled through the ridged plastic that supports the flexible plastic of the air cushion. A short length of plastic tubing was glued to this hole. The chosen pressure sensor fits snugly into this tubing. See Fig. 4.

This implementation is functional, but the toxicity of the glue must be assessed as part of the future work in this project.

The piezoelectric pressure sensor only draws approximately 3 mA and so is powered directly by one of the development board's digital I/O ports (Digital I/O pin 7).

16.4 Micro SD card and micro SD breakout board (MIKROE-429)

A micro SD breakout board with on-board high frequency noise filtering was chosen (MIKROE-429, MikroElektronika, Serbia). This filtering is provided by an on-board ferrite bead and a capacitor. The MIKROE-429 was the physically smallest micro SD breakout board with an on-board filter that was commercially available. This module communicates on the SPI bus.

An S200u (Swissbit, Switzerland) micro SD memory card was purchased as this was reported to have very low current consumption. However, two of these cards received from Mouser Electronics (TX, USA) malfunctioned on their first day of use. A generic/unbranded micro SD card is currently in use instead.

It should be noted that a micro SD card ordinarily draws some current when the card is present and the micro SD breakout board is powered. The amount of current which is constantly drawn increases considerably when the card is initialised, and increases again when a read/write command is given. As a result, the micro SD card is only powered and initialised in this device when is it needed, and is

uninitialised and power is removed as soon as possible after a write operation has completed.

The terms “initialised” and “uninitialised” are something of a misnomer. Every time the card is to be written to, the card must be initialised by the firmware. Before power is removed from the card, it must be always be uninitialised by the firmware. Initialisations permit the firmware to access the file system of the card. If the card is not uninitialised before the power is removed, the filesystem becomes inaccessible by the firmware.

The micro SD card and breakout board are powered via the voltage regulator on the development board. The development board controls the power supplied to the breakout board via a high-side switch attached to digital I/O pin 9. Q2, R2, Q3 and R3 form the high-side switch for this peripheral. A high-side switch was preferred over a low-side switch as parasitic currents continued to flow when a low-side switch was tested.

The micro SD card and micro SD card breakout board are precarious:

- The micro SD card required 3.3V to operate. The entire device runs on 3.3V. There is a risk that the batteries will be too depleted to operate the micro SD card after some weeks of use.
- The micro SD card is, by design, is attached to the breakout board via pressure contacts. These points of contact may fail.

16.5 Real Time Clock (RV8523)

This RTC was chosen due to its low voltage requirements. It communicates on the I²C bus. The RTC is powered via the voltage regulator on the development board. The development board controls the power supplied to the RTC via a low-side switch attached to digital I/O pin 8. Q1 and base resistor R1 form this low-side switch. The Darlington Pair selected (Q1) provides the RTC with better isolation from ground than a single BJT could. The datasheet for the RV8523 claims that the integrated circuit can operate perfectly with a supply voltage as low as 1.8V.

This RTC appears to suffer clock drift over time. Future work involves analysing this and determining if this drift is acceptable or if a replacement RTC is required.

16.6 Memory Dump Button

After the patient has returned the device, the clinician/researcher must ensure that all of the timestamps that are present in the internal EEPROM memory are moved to the micro SD card. The micro SD card can then be removed from the device and the data can be retrieved using a standard micro SD card-reader. In order to invoke this movement of data from the internal memory to the micro SD card, a button has been included in this design. This button is slightly submerged, and so it cannot be accidentally pressed. The firmware ensures that the data is only moved if this recessed button is held down.

This button is known as the “Memory Dump Switch”.

R5 is a pull-down resistor that keeps digital I/O pin 4 low. The “Memory Dump Switch” pulls digital I/O pin 4 high when pressed.

16.7 Tilt Switches (RBS040110)

Interrupt 0 of the microcontroller is connected to digital I/O pin 2 of the development board. This interrupt is used to wake the device from the low-power/sleep mode. Any change to the state of this pin wakes the device. Two tilt sensors are mounted in different orientations on the facemask of the breath stacker. RBS040110 (OncQue, Taiwan) sensors were chosen as they are small, lightweight and appear to be very robust. These switches are wired in parallel with each other, and connected to digital I/O pin 2 with a pull-down resistor (R4). R4 is 33M Ω , and so very little current flows even when one or both of the tilt sensors are closed (less than 0.1 μ A).

Any type of vibration detection switches can be used instead of these tilt switches. Tests indicated that these switches are well suited to this application. The mechanical movement of the switches suits the movements that the mask experiences when the breath stacker is picked up and when it is in use. These switches are sufficiently able to wake the device and were not excessively sensitive to movement.

16.8 Battery (LS17500CNA)

It is estimated that the device will require approximately a 1.5Ah battery in order to survive three months with a patient. A button cell is physically small and thus desirable for this design. Unfortunately, the highest capacity button cell that could be found was only 1Ah. Two or more cells could have been used for the prototype. The LS17500CNA (SAFT, France) was selected as it is a single 3.6Ah cell. It is a non-rechargeable Li-SOCl₂ cell which is physically larger than two button cells, but is robust as it is a single cell. It is 3.6V, so very little energy will be dissipated through the voltage regulator on the development board. It has a maximum recommended continuous current of 130mA, which is sufficient for this prototype.

Further research is required to verify if the battery chosen is safe for medical device applications. Future work also involves sourcing a physically smaller cell that offers sufficiently high capacity.

16.9 Capacitors

Due to the nature of the ICs in this circuit, a certain amount of high-frequency filtering is required. C1 was added over the development board's regulated 3.3V output and C2 was added over the development board's voltage input (over the battery terminals). These capacitors filter out any noise produced when the device is initially powered up, and filter out any noise produced when the peripherals are powered up. Both C1 and C2 are 22 μ F 10V tantalum capacitors.

16.10 MIKROE-480

This is a flash memory module that was considered for use in this device. It contains the M25P80 Serial Flash IC, and the PCB has an on-board decoupling capacitor and two pull-up resistors. The memory module communicates on the SPI bus.

This module was initially preferred over micro SD card as it draws less current, does not need to be initialised and uninitialized, does not require transistor-controlled power switches, and is not spring-contact dependent like the micro SD card. For these reasons, it is more reliable. The IC itself has its own low-power/deep-sleep mode in which the module only draws 1 μ A.

Code was written which interfaced with this module and initial tests showed promising results. The current consumption and functionality of both this module and the micro SD module were compared. There were many benefits to the M25P80. However, data retrieval was a concern. The micro SD card can be easily removed from the device and plugged into a standard card reader. This is intuitive for most researchers. The M25P80, in comparison, requires the researcher to plug the device into a PC. Custom software would need to be designed so that any researcher can easily retrieve the data. An Arduino sketch was written for this purpose, but it must be converted into an executable for general use. In addition, the I/O pins of the development board are not easily assessable and so some interface would also need to be designed.

Due to the intuitive nature of the micro SD card, the M25P80 memory module was not selected for use with this prototype. Future work involves researching a wireless communications interface for the device, such as Bluetooth. Should a wireless interface be implemented, a solid state memory module such as the M25P80 could considerably be used.

16.11 Wireless Communications

Due to the physical size constraints, power constraints, and project time constraints, no wireless communications modules were considered for use with this device.

Future work involves looking into adding such a feature so that the researcher can easily retrieve the data from the device.

Power concerns

This device is intended to reside with a patient for up to three months. As a result, measures had to be taken to reduce the power consumption.

The micro SD card is the largest consumer of power, and draws approximately 15mA when data is being written to the card. Even when the card has only been initialised and data is not being written to it, it still draws approximately 10mA.

In order to minimize the current, the decision was made to utilise the internal EEPROM as much as possible. The timestamps are thus recorded initially to internal EEPROM, and the micro SD card is only powered up and initialised when either the EEPROM is full or when the memory-dump button has been held down.

It was for this reason that the MIKROE-480 memory module was initially considered. It draws substantially less current than a micro SD card. However, as explained in the Hardware Related Technical Details, the intuitive interface of the micro SD card was preferred over the MIKROE-480 memory module.

In order to further reduce the power consumed by the device, the piezoelectric pressure sensor and the RTC are both also powered down when they are not required.

The board itself can be put into a low-power mode. When all of the peripherals are switched off and the board is in low-power mode, the entire device draws approximately 20 μ A.

The device can thus be in one of four states:

1. Asleep: Development board in low-power mode. All peripherals switched off.
2. Awake and Detecting: Board is in full power mode. Piezoelectric pressure sensor is switched on. The device is monitoring the piezoelectric pressure sensor and will react if sufficient pressure is detected. If sufficient pressure is not detected, the device will timeout; power will be removed from the piezoelectric pressure sensor the development board will return to low-power mode.
3. Usage Detected: When sufficient pressure is detected by the piezoelectric pressure sensor for a sufficient period of time, it is assumed that the breath stacker has been used. The piezoelectric pressure sensor is briefly switched off. The RTC is powered on and the current time is acquired. This time is written to EEPROM. The RTC is then powered off and the piezoelectric pressure sensor is switched back on, ready to detect another usage instance.
4. Memory-dump: When the EEPROM is full, or when the memory-dump button has been pressed and held down, the timestamps are read back from the EEPROM. These are packaged into pages, and the micro SD card is powered up and initialised for brief periods of time, just long enough to write each page of timestamps. The piezoelectric pressure sensor and the RTC remain powered off during these memory-dump operations.

Estimations were made about the amount of time that the device would spend in each state. The amount of current drawn during each process was measured. A rough estimate concluded that a 1.5Ah battery should be sufficient to keep the device alive for up to three months.

Implementation

Considering the small number of devices that are required in the near future, the decision was made to try and implement all the devices using commercially available modules and components. The prototype is crudely implemented and the components are held together with electrical tape. The primary power switch is also crudely implemented; it consists of two wires that can be twisted together.

This design is acceptable as a prototype but the robustness, aesthetics, size and weight need to be addressed as part of the future work.

18.1 Piezoelectric pressure sensor

A hole was carefully drilled through to the air cushion of the facemask. Flexible tubing was fitted snugly into this hole and was glued into place. The nozzle of the piezoelectric pressure sensor was snugly fitted into the open end of the tubing. The facemask was then re-inflated.

The piezoelectric pressure can be glued into the plastic tubing if desired.

A sufficiently long wire was soldered directly to the pins of the piezoelectric pressure sensor. These wires were soldered directly to the relevant ports on the development board's PCB.

18.2 Tilt switches

The tilt switches were taped in two different orientations onto the outer edge of the facemask's inlet. Tests indicated that these switches are well suited to this application. The mechanical movement of the switches suits the movements that the mask experiences when the breath stacker is picked up and when it is in use.

The tilt switches are wired in parallel, and the wires are soldered directly to the ports of the development board.

18.3 Memory Dump switch

The PCB of the RTC contained a small hole. This hole was expanded and the pushbutton switch was glued with the pusher facing into this hole. This PCB is sufficiently thick, so the button is protected from being accidentally pressed. A pin, needle, or similarly long tool can be used to reach the pushbutton.

The legs of this switch are carefully soldered directly to resistors R4, R5 and to the ports of the development board.

18.4 Development board, RTC, SD breakout board, resistors, transistors & capacitor

The ports of the development board were carefully soldered directly to the legs of the transistors, resistors, and to wires which interconnected the ports to the peripherals. The RTC and micro SD breakout board were neatly laid side-by side, and the resistors and transistors were carefully sandwiched between these and the development board. Capacitor C1 which lies over the voltage regulator's output was also soldered directly to the ports and was also neatly squeezed into the limited space between these boards. (See Fig. 9).

These components were carefully insulated from each other and were then taped together. (See Fig. 9).

18.5 Battery and capacitor

Wires were soldered to the battery terminals and to capacitor C2. The wire attached to the negative terminal was directly soldered to the development board. The wire attached to the positive terminal has a wire soldered to it. A wire was also soldered to the Vin port of the development board. These wires can be simply twisted together to complete the circuit and power up the device. This switch system is crude, but it removed the need for an additional switch. These wires can be soldered together and insulated if required, or a latching switch can be implemented in the future if required.

The capacitor was taped to the battery, and the battery was taped along the long edge of the other peripherals.

18.6 Mounting to the facemask

The tilt sensors and piezoelectric pressure sensor were mounted to the mask as explained above. The remaining components were taped together and were then taped to the lower part of the outer face of the mask (See Fig. 2 and Fig. 3). The way in which the battery is mounted to the development board/RTC/micro SD card module permits a slight flexibility and so the device curves slightly along with the curvature of the face of the mask. (See Fig. 2).



Fig. 1. Breath stacker apparatus with assembled prototype attached to facemask.



Fig. 2. Side view of assembled prototype attached to facemask



Fig. 3. Rear view of assembled prototype attached to facemask.

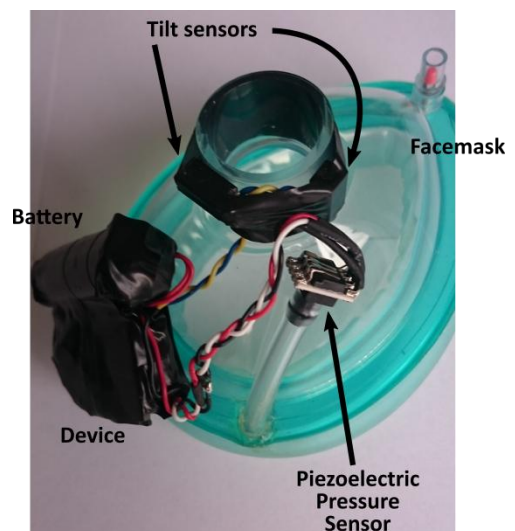


Fig. 4. Partially disassembled prototype.

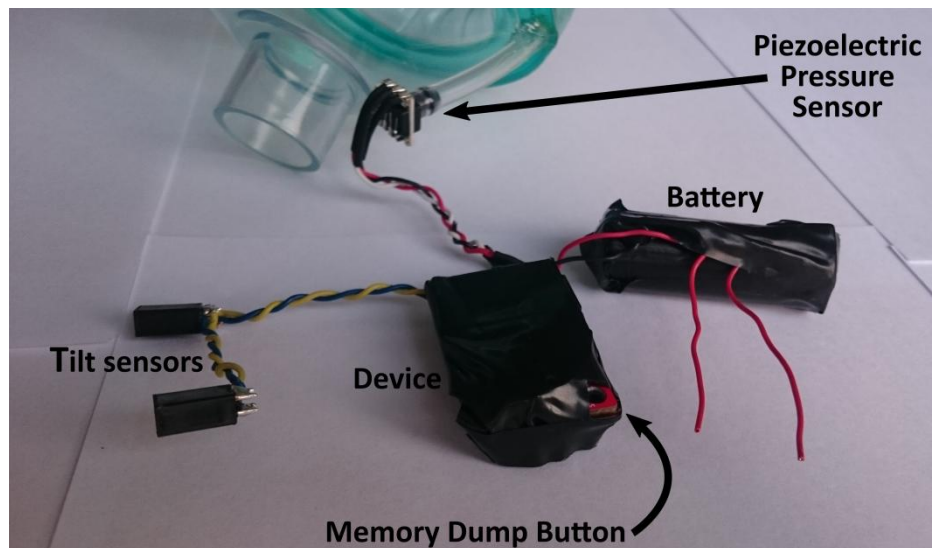


Fig. 5. Partially disassembled prototype.

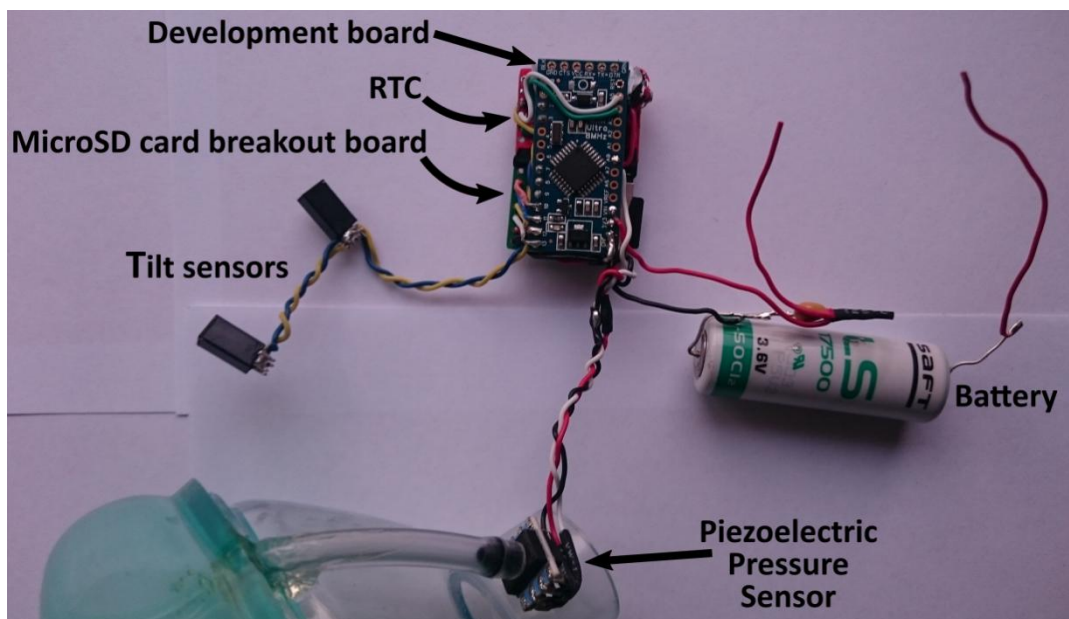
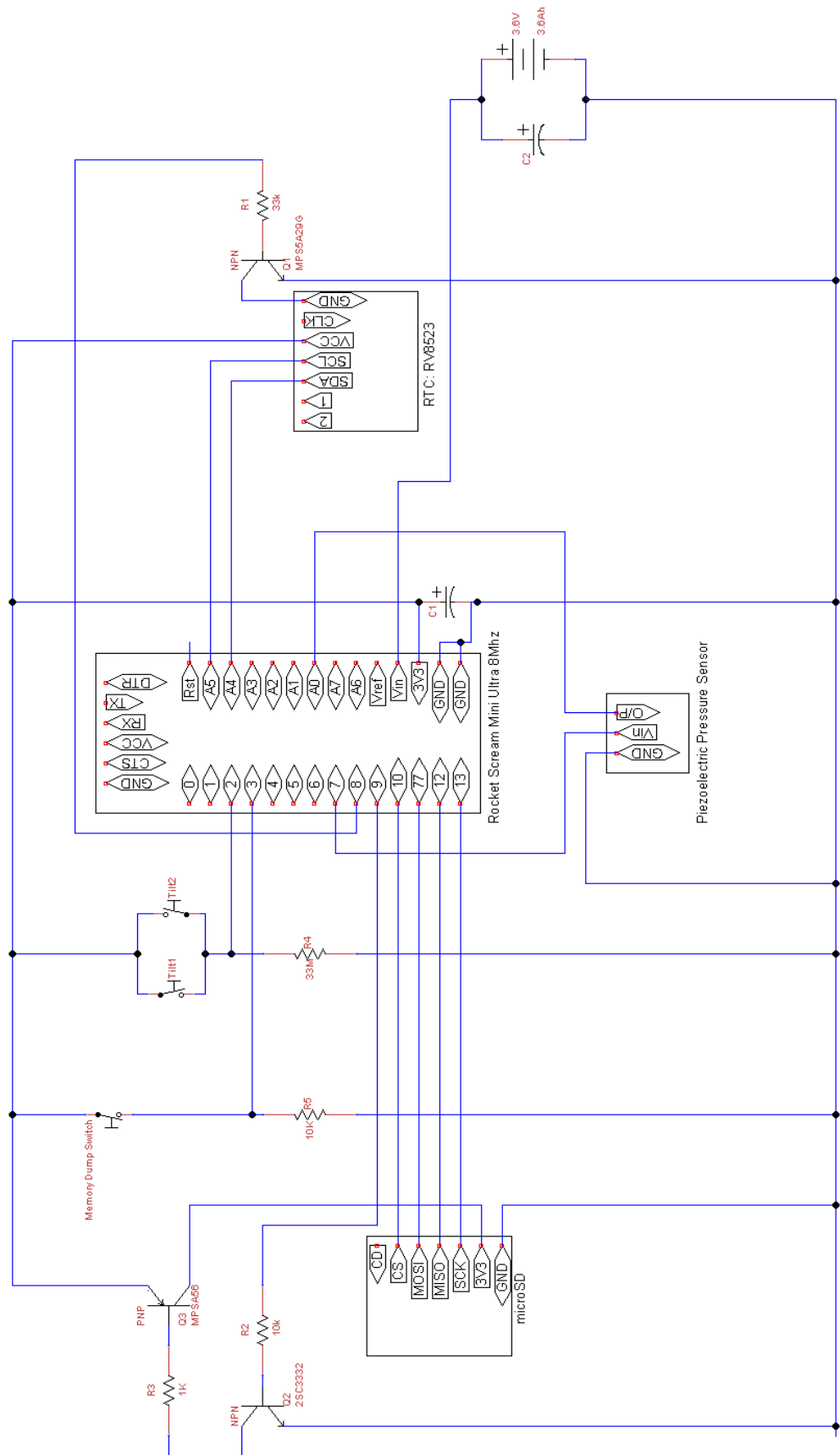


Fig. 6. Disassembled prototype.

Schematic



Physical layout of components for prototype

As explained in the Implementation Section, the RTC and micro SD breakout board were neatly laid side-by-side. The resistors, transistors, memory dump switch and one of the capacitors were carefully laid out and sandwiched between RTC/micro SD module and the development board. The layout of these components was optimized to minimize the bulkiness of the device and to minimise the lengths of interconnecting wires where were required. Fig. 7 and Fig. 9. show the physical layout of the components in this prototype.

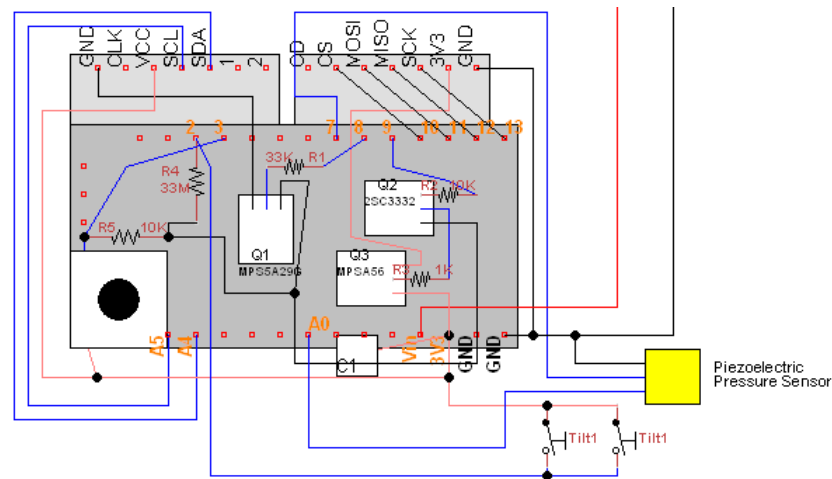


Fig 7. Layout of components for prototype. C2 and Battery omitted for clarity. Wiring between RTC, micro SD breakout board, Development board and other components can be seen.

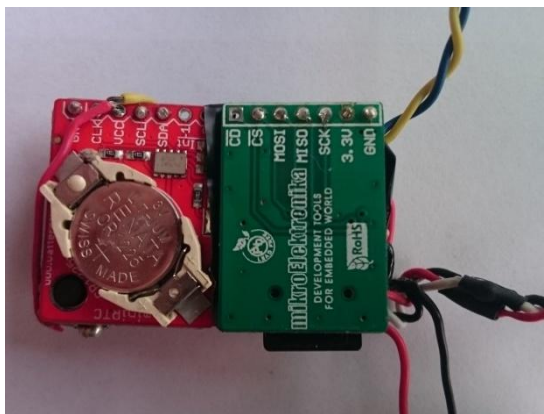


Fig. 8. RTC and micro SD breakout board attached to Development board.

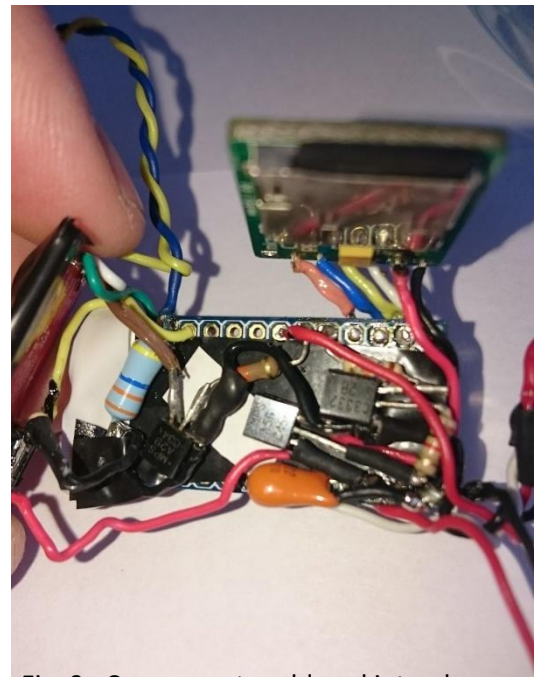


Fig. 9. Components soldered into place as described in Fig. 7.

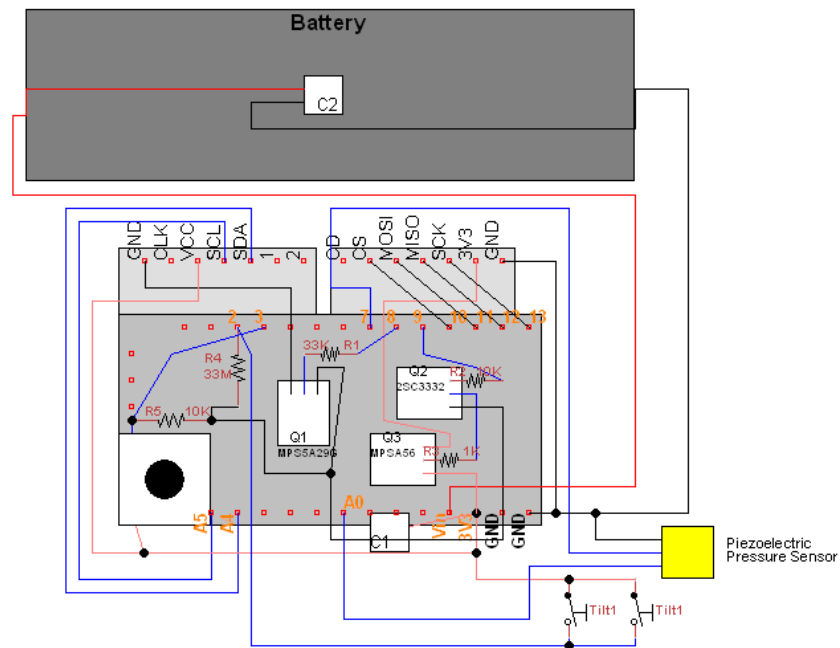


Fig 10. Layout of components for prototype. Wiring between RTC, micro SD breakout board, Development board, Battery and other components can be seen.



Fig.

Components soldered into place as described in Fig. 10.

11.

Firmware Related Technical Details

Two algorithms have been designed for this device; one *Standard Firmware* and one *Debug Firmware*.

The standard firmware tracks:

- Time and date when the device is used
- The number of times the internal EEPROM capacity was filled
- If, after the EEPROM capacity was filled, the data failed to transfer from EEPROM to SD card

The debug version was designed to collect a great deal more data than the standard version. As the device was being tested by the developers, it became apparent that this additional data would greatly aide in debugging the software and testing the device.

In addition to the standard data, the debug firmware also tracks:

- Time and date when the device is powered up
- Time and date when the device sleeps
- Time and date when the device wakes
- Time and date when the piezoelectric pressure sensor detects a pressure above a desired threshold
- Time and date when the piezoelectric pressure sensor drops below a desired threshold
- Time (in milliseconds) between the primary pressure threshold being reached and the pressure dropping below the secondary threshold
- Time and date when the EEPROM runs out of capacity
- Time and date when the memory-dump button is pressed
- Time and date when the memory-dump button is held down
- Time and date when DATA.txt has is saved to micro SD card
- Time and date when any pages of data are written to micro SD card
- Time and date when DATA.csv is saved to micro SD card
- Time and date when data fails to write to micro SD card

The primary benefit of this additional tracking is to see how often the device wakes, and to track if any unexpected events occurred.

Unfortunately however, the debug firmware is not power sensitive. The micro SD card is powered and initialised each time one of these additional values is stored. All of these events are stored to a file on the micro SD card called DEBUG.txt.

In order to minimize the time that the micro SD card was powered on and initialised, only short codes were recorded to file.

The full explanation of algorithms can be seen below. Flowcharts have been included to help the reader better understand the algorithm.

21.1 Firmware features

Upon startup, the firmware firstly configures the I/O pins. All of the output pins are pulled low, and thus each peripheral is switched off.

The firmware then begins the main loop function. The first command of this loop puts the device into a low power or “sleep” mode. The primary loop stalls/exits at this point.

If the development board detects any change on interrupt 0 (digital I/O pin 2), the board wakes up and primary loop resumes from the point where it was stalled. Digital I/O pin 7 is switched high and thus the piezoelectric pressure sensor is powered up. A timer begins in which the memory dump button and the piezoelectric pressure sensor are monitored.

If the device is left idle, the piezoelectric pressure sensor is powered down, the timer loop then exits and the primary loop restarts. Again, at the beginning of the loop, the firmware issues the commands which put the device to a low power or “sleep” mode. The primary loop stalls/exits n.

If sufficient pressure is detected by the piezoelectric pressure sensor while the device is awake, an inner loop begins. This loop exits if the pressure drops below an empirically determined value, or exits after an empirically determined amount of time (e.g. 700 ms). If the loop exited due to the inner timer elapsing, the pressure must have remained sufficiently high and so the current date/time is recorded to EEPROM. If, however, the loop exited due to the pressure dropping, nothing is recorded.

If a timestamp is recorded, the device will stay awake for a longer duration as it appears as if the breath stacker is in use.

Should the timer elapse, the primary loop will again restart and the device will return to low-power/”sleep” mode.

Any time that the device is awake and a usage is detected, the next available EEPROM address is retrieved from records stored in EEPROM address 00 and EEPROM address 01. These records are updated every time a timestamp is saved to EEPROM. This technique ensures that the next available EEPROM address is always available even if the device suffers from a brown out or temporary power loss. Further details are explained in a subsequent section.

If the internal EEPROM runs out of capacity, the firmware attempts to move all of the EEPROM records to micro SD card. The address records stored in EEPROM address 00 and address 01 are then reset to their minimum values. Thus when the next timestamps are recorded, each address of the EEPROM is incrementally overwritten, starting again from the lowest possible address. Further details are explained in a subsequent section.

As explained in the Hardware Related Technical Details section, the micro SD card and module are potentially likely to fail. As a result, any attempts made to move the timestamps from internal EEPROM to micro SD card might fail. Every time the

internal EEPROM runs out of capacity, a counter which resides in EEPROM address 02 gets incremented. This is used to track the total number of timestamps that were recorded. Thus, the total number of timestamps that were recorded can be tracked. Even if some data is lost, the number of times that the breath stacker was used is still a valuable piece of information to a researcher or clinician. This is further explained in a subsequent section.

If the memory-dump button is held down for a specific amount of time (e.g. 1 second) while the device is awake, the firmware attempts to move all of the data that is contained in the EEPROM to micro SD card. If this write is successful, the address records stored in EEPROM address 00 and address 01 are reset to their minimum values. Thus when the next timestamps are recorded, each address of the EEPROM is incrementally overwritten, starting again from the lowest possible address. If this write was not successful, the address records are not reset.

If any attempt to write to micro SD card fails, a flag is stored to EEPROM address 03.

When the memory-dump button is held down for a specific amount of time (e.g. 1 second) while the device is awake, the firmware attempts to create/update two files on the micro SD card (or three files if the Debug Firmware is used). These files are:

1. DATA.txt – This file contains information such as the total number of timestamps that were recorded by the device, and specifies if any attempts to write to the micro SD card failed.
2. DATA.csv – This file contains the timestamps.
3. DEBUG.txt – This file is only created by the debug version of the firmware. It contains the additional information that is collected by the debug firmware, such as the time at which the device woke, the time at which the device went to sleep, etc.

Digital I/O pin 9 controls the power to the micro SD card module. This is only powered up and the card is only then initialised when data is ready to be written to micro SD card. The card is uninitialised and powered down as soon as a write attempt has completed.

Digital I/O pin 8 controls the power to the Real Time Clock (RTC). This is only powered up when the current time must be captured, such as when a usage is detected. It is powered down as soon as the current time has been acquired by the firmware.

Digital I/O pin 7 controls the power to the piezoelectric pressure sensor. This is powered up when the device is woken, and is powered down just before the device goes back to sleep. It is also powered down at times while the device is awake but the firmware is busy, such as when the data is being written to micro SD card.

21.2 Pressure Detection Region

The analogue reading returned by the piezoelectric pressure sensor fluctuates while the breath stacker is in use. This is due to the physical movements of the breath stacker and the physical movements of the patient. A relatively high reading was

chosen as the primary pressure threshold. This is reading is only reached when a relatively high pressure is placed on the cushion of the facemask. Once this primary threshold has been reached, the analogue reading must remain above a secondary threshold, which is lower than the primary threshold, in order for a usage to be detected. This lower threshold allows for pressure fluctuations due to physical movements. This detection region ensures that the device less likely to erroneously detect a potential usage, and is able to handle the physical pressure fluctuations. These pressure thresholds were empirically chosen.

21.3 Memory usage

The microcontroller has 1024 bytes of internal memory. Each timestamp consists of 6 bytes, 1 byte for each of the following: day, month, year, hour, minute, second. As the year is contained in a 1 byte space, the maximum year that this device can accurately record is the year x225. It is assumed that x is always 2 here. It is assumed that this device will not be in operation up until or after the year 2225, and so the decision was made to store the year as 1 byte to make the most of the limited internal EEPROM storage space.

21.4 EEPROM Address Records

A global variable called “EEPROMAddress” is used to track the next available EEPROM address. Each time a timestamp is ready to be recorded to EEPROM, the data is stored into the EEPROM address location contained in this global variable.

In order to mitigate the risk of data loss due to brown out or temporary power loss, a record of the next available EEPROM address is stored EEPROM address 00 and address 01. Each time a timestamp is ready to be recorded to EEPROM, the global variable “EEPROMAddress” is firstly updated using the data stored in address 00 and address 01.

EEPROM address 00 is known as the “EEPROMAddressMultiplier” and EEPROM address 01 is known as the EEPROM address offset. Every possible EEPROM address can be stored into these two bytes.

“EEPROMAddress” is calculated as follows:

$$\text{EEPROMAddress} = \text{EEPROMAddressMultiplier} * 256 + \text{EEPROMAddressOffset}$$

i.e. $\text{EEPROMAddress} = (\text{value in Address 00}) * 256 + (\text{value in Address 01})$

The first two bytes of the EEPROM (address 00 and 01) are reserved for this purpose. These two bytes are known as the “Address Records”.

Each byte can store a maximum value of 255, and so the greatest possible EEPROMAddressOffset is 255. As this implementation uses a development board with 1024 bytes of EEPROM capacity, the greatest EEPROMAddressMultiplier that

can be reached is 3 as $3 \times 256 + 255 = 1023$. The firmware can detect when the EEPROM capacity is full. When that occurs, an attempt is made to write the timestamps that are contained in the EEPROM to a file which resides on the micro SD card. The details of this procedure are explained in the next section.

The Address Records could alternatively have been directly stored as a binary, hexadecimal, or decimal value. However, three bytes (and so three memory addresses) would have been required to directory store the decimal equivalent value ranging from 0 to 1023. This chosen system can easily store the entire range of EEPROM address numbers.

Future work involves optimising the Address Records system to better suit an embedded software environment.

21.5 EEPROM capacity full procedure

When the EEPROM becomes too full to be able to store another timestamp, an attempt is made by the firmware to move all of the EEPROM records to a file on the micro SD card. Before this attempt is made, a counter which resides in EEPROM address 02 is incremented. This counter tracks the number of times that the EEPROM ran out of capacity.

In order to mitigate the risk of data loss due to card failure, and in an attempt to optimize the amount of time that the micro SD card spends power up and initialised, the data is written to the card in batches. An integer number of complete timestamps are gathered into an array; this array is known as a page. The page-size was chosen to be 258 bytes, which is sufficient space for exactly 48 6-byte timestamps. When one page has been buffered, the micro SD card is powered up and initialised. The entire page is written to DATA.csv. The micro SD card is then uninitialised and powered down. The page array is then overwritten with the next batch of timestamps. The micro SD card is subsequently powered and initialised, and the data in the page is again written to DATA.csv. This process continues until all 1024 bytes (or all 170 timestamps) have been written to the micro SD card.

This paging method means that the micro SD card is not powered while the data is being read from EEPROM. This technique marginally reduces the amount of time that the micro SD card spends powered and initialised. This technique was favoured as it marginally increases the longevity of the batteries which drive the device.

If the micro SD card fails to write any one of these pages, the entire process is aborted. It is assumed that the micro SD has come loose or has failed entirely. If this occurs, a flag is recorded to EEPROM address 03 which indicates that a page-write procedure failed.

Regardless of whether the EEPROM was successfully dumped to DATA.csv or not, the Address Records are set back to their minimum values. EEPROM address 00 (the EEPROMAddressMultiplier) is set to 00, and EEPROM address 01 (the EEPROMAddressOffset) is set to 04. Note that EEPROM addresses 00 to 03 are reserved for the Address Records, the capacity-filled counter, and the SD card failed flag, respectively. Thus, the minimum EEPROM address that is available for timestamps is EEPROM address 04.

The EERPOM is thus reused; the data in each EEPROM address is sequentially overwritten as the breath stacker is used. This is ideal if all of the records in the previously full EEPROM were successfully moved to micro SD card. However, data loss will now occur if the write to micro SD card was unsuccessful. This is the reason for the counter in EEPROM address 02. Even if the card failed, the clinician or researcher can at least find out the number of timestamps that were recorded by the device. This will provide some evidence about the number of times that the breath stacker was used.

An attempt is made to write the data to the micro SD card every time that the EEPROM runs out of capacity. A micro SD card that had previously failed may potentially become usable again due to a range of external factors. DATA.csv is appended during every successful write operation.

21.6 Invoked Memory Dump

When the device is awake and the memory-dump button is held down, the firmware beings the process of moving any timestamps that are in the EEPROM to the micro SD card. It is assumed that, if the micro SD card had failed, the researcher or clinician can now insert a new card or take any steps required to ensure that the micro SD card and card module are working correctly.

The invoked memory dump is a multistage process:

1. The number of times that the EEPROM ran out of capacity is read from EEPROM address 02.
2. The flag specifying if the micro SD card ever failed is read from EEPROM address 03.
3. The number of timestamps that are currently in the EEPROM is determined.
4. The RTC is briefly powered and the current date and time is acquired. The RTC is then promptly powered down.
5. The micro SD card is powered up and the card is initialised.
6. An attempt is made to write DATA.txt. DATA.txt is an information file which specifies the time at which this invoked memory dump process began, specifies the total number of timestamps that were recorded by the device, and states if the micro SD card ever failed when a write operation was being attempted.
7. If the micro SD card failed while an attempt was being made to write DATA.txt, the firmware aborts the invoked dump operation. It returns to the main loop and resumes normal operation.
8. If, however, DATA.txt was written successfully, the invoked dump process moves on to the next stage.
9. If the micro SD card ever failed when the EEPROM had run out of capacity, an attempt is now made to write the entirety of the EEPROM to micro SD card. Some timestamps that were recorded before the Address Records were reset may still be in the EEPROM if they were not yet overwritten. Thus, the clinician or researcher will recover the greatest number of timestamps that are available.

10. If the micro SD card did not fail when the EEPROM ran out of capacity, or if the EEPROM never ran out of capacity, an attempt is made to only write the timestamps that are currently contained in the EEPROM to micro SD card.
11. In order to mitigate the risk of data loss due to card failure, and in an attempt to optimize the amount of time that the micro SD card spends power up and initialised, the timestamps are written to the card in batches. An integer number of complete timestamps are gathered into an array; this array is known as a page. The page-size was chosen to be up to 258 bytes, which is sufficient space for up to 48 6-byte timestamps. When one page has been buffered, the micro SD card is powered up and initialised. The entire page is written/appended to DATA.csv. The micro SD card is then uninitialised and powered down. The page array is then overwritten with the next batch of timestamps, if any remain in the EEPROM. The micro SD card is subsequently powered and initialised, and the data in the page is appended to DATA.csv. This process continues until all of the data has been written to the micro SD card.
12. This paging method means that the micro SD card is not powered while the data is being read from EEPROM. This technique marginally reduces the amount of time that the micro SD card spends powered and initialised. This technique was favoured as it marginally increases the longevity of the batteries which drive the device.
13. If the micro SD card fails to write any one of these pages, the entire invoked dump process is aborted.
14. If and only if all of the available timestamps have been written to DATA.csv, the memory records are reset to their minimum values. The function that controls the invoked dump exits and the primary loop resumes.

21.7 SD card failure detection

As explained previously, the micro SD card can be precarious. It is important to detect when the micro SD card is missing or has failed. Detection and mitigation prevents unnecessary delays in the code and potentially reduces current consumption if a micro SD card has failed. Ordinarily, SD cards should indicate a TRUE signal when the card is initialised. However, the generic/ unknown brand micro SD card that is currently in use behaves with some oddities. This card never returns this TRUE signal, even though it may in fact have initialised correctly. The firmware has been modified to support any cards which do not return this TRUE signal.

Instead of relying on the detection of that TRUE signal, the firmware checks that the files have been created or have opened correctly every time some data is to be written to or appended to a file. If any file fails to be created or fails to open, it can be assumed that the card has failed.

In addition to this, the firmware also monitors the time it takes to write a timestamp to micro SD card. If this is excessively long (greater than 80 ms), then it can also be assumed that the card has failed.

When the date/time records are being read from the EEPROM and written to micro SD card, the data is batched into pages. Only one page is written at a time, and only

one record written at a time. These failure-checks occur every time DATA.txt, DATA.csv and DEBUG.txt are created/opened and every time a timestamp is written to DATA.csv and DEBUG.txt.

21.8 Libraries

The following libraries are used with this device:

SD.h	MODIFIED Arduino SD library
avr/sleep.h	Atmel AVR sleep and power management library
LowPower.h	Rocket Scream sleep and power management library
EEPROM.h	Arduino EEPROM handling library
Wire.h	Arduino Wire library
RV8523.h	Watterott RV8523 RTC library
SPI.h	Arduino Serial Peripheral Interface library

The standard SD library was modified to introduce an *sd.stop()* function. This allows for graceful termination of communications with the micro SD card. Without this function call, the micro SD card cannot re-initialise after it power has been removed and subsequently returned. Details about this modification are available here: <http://forum.arduino.cc/index.php?topic=60513.0> (November 2016).

21.9 Differences in Debug Firmware

The debug version of the firmware collects all of the same data as the standard firmware, plus some additional data that can aide in debugging the device. The debug data is not written to EEPROM, but is instead written directly to the micro SD card. Accordingly the micro SD card is powered, initialised, written to, uninitialised and powered down every time an event occurs that is recorded by the debug firmware. The micro SD card thus spends a great deal more time powered up and initialised than it would be in the standard firmware.

In order to ensure that standard operation is not negatively affected by these additional steps, every write to DEBUG.txt is tailored to be as quick as possible. Attempts to write to DEBUG.txt will cease entirely if an attempt to write to this file fails even once. Such a failure raises a flag which is recorded to EEPROM address 03. The value in EEPROM address 03 is:

- 00 if the firmware never attempted to or never failed to write to DATA.csv, and never failed to write to DEBUG.txt.
- 01 if the internal EEPROM ran out of capacity and an attempt to write to DATA.csv failed.
- 02 if the firmware never attempted to or never failed to write to DATA.csv, and an attempt to write to DEBUG.txt failed.
- 03 if the internal EEPROM ran out of capacity and an attempt to write to DATA.csv failed and an attempt to write to DEBUG.txt failed.

If the value stored in EEPROM address 03 is greater than 1, no debug data is collected. Attempts to do so after the card has failed can slow down the operation of the device and negatively impact the standard operating procedures.

When the device is awake and the memory-dump button is held down, the firmware begins the process of moving any timestamps that are in the EEPROM to the micro SD card. This proceeds in the same manner in both the standard firmware and the debug firmware, however DATA.txt will contain additional information if the value stored in EEPROM address 03 is greater than 1. Instead of only specifying if the SD card failed when the EEPROM was filled, it will also specify if the SD card failed during an attempt to write a debug message to the SD card.

Algorithm Walk-Through

This section provides a walk-through of the Firmware. Please refer to Section 11 (Algorithm Flow Charts) and Section 12 (Arduino Code) while reading this section.

22.1 Pre-compilation directives

Load required libraries.
Assign I/O pins.
State user-controlled variables.
Instantiate all other global variables.

22.2 Functions

22.2.1.1 *void setup()*

Set the pin modes of the I/O ports and set the output states.
- Power to each of the peripherals is set to LOW (OFF)

22.2.1.2 *void loop()*

sleepNow() function is called firstly. This function puts the device into deep-sleep mode.

When interrupt pin changes from high to low or low to high, device wakes up. The number of milliseconds since the device was started is recorded to a variable called “stayAwakeTimerBegin”.

Power is supplied to the piezoelectric pressure sensor.

A while loop begins in which the analogue signal from the pressure sensor is monitored, and the state of the button which invokes EEPROM-to-SD card memory dump is monitored.

The while loop exits if a certain time elapses. This variable is “stayAwakeTime”, and is originally set to 3 seconds.

Within each iteration of this loop:

- The analogue signal from the piezo sensor is read and the current state of the button is read.
- If the state of the button has changed compared to its previously recorded state, a record is taken of the number of milliseconds since the program began.
- If the button is HIGH (i.e. the button has been pressed) and the button has been held down for a certain amount of time (“buttonHoldTime”), then *invokedEEPROMdump()* is called. *invokedEEPROMdump()* will check to see if there are any date/time records in the EEPROM and, if so, will attempt to write them to micro SD card.
- The state of the button in each iteration is recorded into a variable called “lastButtonState”
- If the analogue signal from the piezo sensor exceeds an empirically defined value (“primaryPressureThreshold”):
 - The number of milliseconds since the device was started is recorded to a variable called “detectionTime”.
 - A flag called “thresholdReached” is set HIGH to record the fact that the primary (or initial) pressure threshold has been reached.
 - A while loop begins in which the pressure reading of the piezoelectric pressure sensor is monitored.
 - The loop exists based on one of two conditions: “pressureDetectedTimer” elapses, or the “thresholdReached” flag is set to LOW.
 - The “pressureDetectedTimer” has been empirically set to 700 ms.
 - Inside the loop, the piezoelectric pressure sensor is monitored and the “thresholdReached” flag is set to LOW if the pressure drops below an empirically defined value called “secondaryPressureThreshold”.
 - This loop allows a valid detection-region, as the pressure may fluctuate slightly during use.
 - If the “thresholdReached” flag is still HIGH after the loop exits, then the loop can only have exited due to the “pressureDetectedTimer” elapsing.
 - The “stayAwakeTimerBegin” counter is reset to the current number of milliseconds since the device was started.
 - If “thresholdReached” is still HIGH:
 - The power supplied to the piezoelectric pressure sensor is set to LOW.
 - The *usageDetection()* function is called, in which the current date and time is stored to EEPROM.
 - The program delays a predetermined time period (“usageDetectionInterval”). This prevents too many date/time stamps from being recorded at any instant when the breath stacker apparatus is in use.
 - The “stayAwakeTime” variable is now set to a new value called “stayAwakeAfterDetection”. “stayAwakeAfterDetection” has been empirically set to 30 seconds. This ensures that an outer loop will now

iterate for a longer period of time as the breath stacker apparatus is actually in use.

- “stayAwakeTimerBegin” is reset to the current time since the device was started.
- Power is restored to the piezoelectric pressure sensor

The outer while loop will iterate until the “stayAwakeTime” elapses with respect to “stayAwakeTimerBegin”. Note that “stayAwakeTime” is initially 3 seconds, and will increase to 30 seconds when the breath stacker apparatus is used.

The piezoelectric pressure sensor is turned off once the outer while loop exits.

“stayAwakeTime” is reset to its shorter value “originalStayAwakeTime”.

The primary loop function *loop()* thus finishes and is subsequently called again. As stated above, the first thing that this loop does is call *sleepNow()* and thus the device goes back into deep sleep mode.

22.2.1.3 *void usageDetection()*

This function is called if the piezoelectric pressure sensor returns an analogue voltage above an empirically decided value (“primaryPressureThreshold”) and remains above another empirically decided (“secondaryPressureThreshold”) value for an empirically determined period of time (“pressureDetectedTimer”). This function requires no inputs and returns no values.

This function calls the *getTime()* function, then the *getEEPROMaddress()* function, and then the *storeToEEPROM()* function. None of these functions are passed any variables.

getTime() determines the current date/time from the RTC.

getEEPROMaddress() determines the next free EEPROM address.

storeToEEPROM() stores the current date/time into the next free EEPROM address.

22.2.1.4 *void getTime()*

This function turns power on to the RTC, gets the current date and time, and stores the 6-byte array to a global array “datetime”. It then turns the RTC power back off. This function requires no inputs and returns no values.

This RTC returns the second, minute, hour, day and month as 8-bit values. It returns the year as a 16-bit value. However, in order to maximize the number of dates/times which can be recorded to the limited EEPROM space, only the

least-significant byte of the year value is stored to the “datetime” array. The rest of the program assumes that the year field of this array is between “00” and “99”. This is acceptable as it is assumed that the device will not be in use past the year 2099.

22.2.1.5 *void getEEPROMAddress()*

This function calculates the EEPROM address that the first byte of the 6-byte date/time record should be written into. This function takes no inputs and returns no values.

The first two bytes of the development board EEPROM are reserved for address records. The first byte is the “EEPROMAddressMultiplier” and the second is the “EEPROMAddressOffset”. Each can only contain up to a maximum value of 225. There are 1024 byte addresses in the EEPROM. In order to track where the next date/time record should go, this function reads these first two bytes and calculates the address. The EEPROM address is the “EEPROMAddressMultiplier” multiplied by 256, plus the “EEPROMAddressOffset”. This value is stored into a global variable “EEPROMAddress”.

The values in address 00 and address 01 are updated by the *storeToEEPROM()* function only after some data has been stored to EEPROM.

22.2.1.6 *void storeToEEPROM()*

This function writes the date/time values in the “datetime” array to the EEPROM. This function takes no inputs and returns no values.

“EEPROMAddress” is a global variable that contains the EEPROM address that the first byte of the date/time record is to be written to. This global variable is incremented by 1 inside a For loop, directly after an element of the “datetime” array has been stored to EEPROM. The loop exits after all the elements of the “datetime” array have been written to the EEPROM.

The current “EEPROMAddress” is then checked. If the EEPROM is now full:

- EEPROM address 02 is read into a local variable called “numDumps”. This value is incremented by 1 and written back to the same memory address. This EEPROM address records the number of times that the EEPROM ran out of capacity.
- The current “EEPROMAddress” is written to a global variable called “maxEEPROMAddress”. This will be used to control the range of EEPROM addresses that will be read and subsequently written to SD card.

- *writeEEPROMtoExternal()* is then called. This function accepts one argument: the number of bytes that must be written to SD card. In this call, the argument is “EEPROMAddress” minus “minEEPROMAddress”. That function returns a 1 if the write was successful, and a 2 if the write failed. The returned result in this case is stored into a variable called “success”.
- If “success” equals 2:
 - The data was not successfully copied from internal EEPROM to SD card.
 - In the standard version of the firmware, value 01 is written to EEPROM address 03. This records the fact that the memory dump failed.
 - In the Debug version of the firmware, value 01 is written to EEPROM address 03 if the Debug functionality is still working as expected. However, value 03 is recorded to memory address 03 if the memory dump failed and the Debug functionality has also failed.
- The EEPROM address records in EEPROM address 00 and address 01 are then reset to their minimum values.

The size of the “datetime” array is then combined with the current Address Offset, and is compared to the EEPROM segment size (which is 255 bytes). If the combined value is greater than 255 bytes, then the next EEPROMAddressOffset value will be too large to store into a single 1-byte EEPROM memory address

- If the combined value is greater than 255 bytes, the current “EEPROMAddressMultiplier” is incremented by 1 and saved back to EEPROM memory address 00.
- The “EEPROMAddressOffset” is incremented by the size of the “datetime” array and decremented by 256.
 - Note that “EEPROMAddress” is calculated at each usage time, and is calculated by reading the “EEPROMAddressMultiplier” from EEPROM address 00 and the “EEPROMAddressOffset” from EEPROM address 01. “EEPROMAddress” = “EEPROMAddressMultiplier”*256 + “EEPROMAddressOffset”.
 - For example:
 - If the previous 6-byte “datetime” array was written into EEPROM addresses 252 to 257, the “EEPROMAddressMultiplier” would have been 0 and the “EEPROMAddressOffset” would have been 252. We can see that the next address to be written to when the apparatus is next used is 258. The “EEPROMAddressOffset” to be recorded for the next usage instance would be $252 + 6 = 258$. However, this value cannot be stored to a single EEPROM address as it is greater than 8 bits. As a result, the “EEPROMAddressMultiplier” now increases from 0 to 1, and the new “EEPROMAddressOffset” is “EEPROMAddressOffset” + “sizeof(datetime)” - 256 = $252 + 6 - 256 = 2$. Now, when the apparatus is used next, the address is calculated as

$\text{"EEPROMAddressMultiplier"} * 256$ +

$\text{"EEPROMAddressOffset"} = 1 * 256 + 2 = 258.$

- The multiplier will increase up to 3 as the EEPROM capacity gets filled. The internal EEPROM capacity will be completely filled before the multiplier ever reaches 4. As previously said if the EEPROM gets completely filled, the device will write all date/time records to the attached micro SD card and will reset the $\text{"EEPROMAddressMultiplier"}$ and $\text{"EEPROMAddressOffset"}$ to their minimum values.

If the EEPROM is not at capacity, and $\text{"EEPROMAddressOffset"} + \text{"sizeof(datetime)"}$ is not greater than 255, then $\text{"EEPROMAddressOffset"}$ is incremented by the size of the "datetime" array.

In any of the above cases, the $\text{"EEPROMAddressMultiplier"}$ and $\text{"EEPROMAddressOffset"}$ are updated such that, when the apparatus is used next, the next available EEPROM address can be calculated based on the values stored in EEPROM address 00 and address 01.

22.2.1.7 *int writeEEPROMtoExternal(int numBytes)*

This function takes in the number of bytes that is to be written to the micro SD card and returns 1 if the write was successful or 2 if the write failed. Initialising and writing to SD card consumes a lot of power. For efficiency and in order to maximize battery life, the data that needs to be written to the micro SD card is first packaged into an array. The card can then be initialised once and the array can be written immediately. This function takes care of packaging the EEPROM records into arrays, and calls the *writePageToExternal()* function.

This array is referred to as a page. The page is 258 bytes in size, and accommodates an integer number of 6-byte date/time records. The page array is a global variable called "dataForExternal" .

"numBytes" is the argument in this function. This is the number of bytes that is to be written from the internal EEPROM memory to the SD card.

"numPages" is the number of pages that can be filled, and this is calculated by dividing "numBytes" by the size of the "dataForExternal" array.

"overflowBytes" is the outstanding number of bytes that do not fit into a full page array.

"EEPROMAddress" is set to $\text{"minEEPROMAddress"}$. The bytes will be buffered starting from this minimum address.

An outer for loop iterates through the number of full pages.

- Inside this for loop is another for loop which iterates through the number of bytes in the page (258 bytes). In the inner for loop the page is filled with bytes from the EEPROM.
- After a page has been buffered, *writePageToExternal()* is called, which writes the buffered page to SD card. *writePageToExternal()* accepts one argument: the number of bytes to be written in this instance.
- *writePageToExternal()* returns a 1 if the write was successful or a 2 if the write failed.
- If *writePageToExternal()* returned a 2, then *writeEEPROMtoExternal()* returns a 2 to the calling function and the function terminates.

The partial page (the “overflowBytes”) is then buffered to the “dataForExternal” array, and *writePageToExternal()* is called again. This time the argument specifies that only the number of “overflowBytes” needs to be written to SD card instead of the whole page as was specified in the previous call. Again, a 1 is returned by *writePageToExternal()* if this write was successful, and a 2 is returned by *writePageToExternal()* if the write failed. If a 2 was returned, then *writeEEPROMtoExternal()* returns a 2 to the calling function and the function terminates.

If the *writeEEPROMtoExternal()* function reaches its final line, then the data was successfully written from EEPROM to SD card. The function returns a 1 to indicate success to the calling function.

22.2.1.8 *int writePageToExternal(int numBytes)*

This function writes a specified number of bytes to the micro SD card. This function takes in the number of bytes that are to be written in this call, and returns a 1 if the write was successful, or returns a 2 if the write failed.

This function switches the I/O port that controls the SD card power switching circuit to HIGH and initialises the micro SD card.

“failedFlag” is initially set to 0.

An attempt is made to open "DATA.csv" which is a file which resides on the memory card. If this file doesn't currently exist, it will be created when the opened file is saved.

If "DATA.csv" opened successfully, we can assume that the SD card powered up correctly and initialised correctly.

- A for loop iterates through “numBytes” in steps of “sizeof(datetime)”.
 - “failedFlag” is checked. If it is 0:
 - The number of milliseconds since the device started is written to “startTime”. This will later be compared to the

time it takes to open the file and write one date/time stamp. This will be used to detect if the SD card has failed.

- A for loop iterates through 6 (or “sizeof(datetime)”) bytes of the “dataForExternal” array.
- Each element is correctly formatted and then written to file.
- The order that the date/time records are stored in is DDMMYYHHMSS, and so the bytes are formatted into DD/MM/YY,HH:MM:SS when being written to file. The comma ensures that the date and the time appear in separate columns in the csv file. The data is stored in the internal EEPROM memory without any leading zeros, and so this loop adds in zeros for clarity.
- The number of milliseconds since the device started is then written to “endTime”.
- Using “endTime” and “startTime”, the time it took to write one date/time stamp can be calculated. If this is greater than 80 ms:
 - We can assume that the card did not power or initialise correctly.
 - “failedFlag” is set to 2.
 - In the Debug version of the firmware, the command is issued to uninitialise the SD card.
- In each iteration of the loop, if “failedFlag” is equal to 2, the data will not be read from EEPROM memory and will not attempt to be written to the SD card.

If the file did not open correctly:

- “failedFlag” is set to 2.
- In the Debug version of the firmware, the command is issued to uninitialise the SD card.

The command is issued to close "DATA.csv" so that any changes to the file will be committed to the SD card.

In the standard version of the firmware (not the Debug version), the command is issued to uninitialise the SD card.

Power to the SD card module is set to LOW.

If “failedFlag” is 0, *writePageToExternal()* returns a 1 to the calling function to indicate success.

If “failedFlag” is 2, *writePageToExternal()* returns a 2 to the calling function to indicate failure.

22.2.1.9 ***void invokedEEPROMdump()***

This function will determine if there are any date/time records in the EEPROM and will attempt to write any date/time stamps to SD card. It accepts no arguments and returns nothing.

EEPROM address 02 is read and is saved to a local variable called "numDumps". This value is a record of the number of times that the EEPROM capacity was filled.

EEPROM address 03 is read and is saved to a local variable called "intermediateDumpFail". This value shows if a previous attempt to write to SD card failed, such as if the EEPROM capacity was filled but the data was not successfully written to SD card.

The number of date/time stamps currently in the EEPROM is determined by calling *getEEPROMaddress()*.

The I/O port that controls the SD card power switching circuit to HIGH and micro SD card is initialised.

An attempt is made to open "DATA.txt" which is a file which resides on the memory card. If this file doesn't currently exist, it will be created when the opened file is saved.

"dataRecordsSuccess" is initialised and set to 0. This will be set to 1 if "DATA.txt" opens correctly, but will be set to 2 if the file does not open. The file will not open if the SD card is missing or fails to power up or initialise.

If "DATA.txt" opened successfully, we can assume that the SD card powered up correctly and initialised correctly.

- *getTime()* is called to determine the current date and time. This value is written to "DATA.txt"
- Information, such as: (i) the total number of date/time stamps, (ii) the number of times the EEPROM capacity was filled and (iii) if the data failed to write correctly when the EEPROM was filled, is written to "DATA.txt".
- "dataRecordsSuccess" is set to 1 to indicate that "DATA.txt" opened successfully
- The command is issued to close "DATA.txt" so that any changes to the file will be committed to the SD card.

If the file did not open correctly:

- "dataRecordsSuccess" is set to 2.

The command is issued to uninitialise the SD card and the power to the SD card module is set to LOW.

If "dataRecordsSuccess" is equal to 2, the function terminates. If it is not equal to 2, the function will proceed to attempt to write the date/time stamps in the EEPROM to SD card.

If “intermediateDumpFail” indicates that the EEPROM capacity was filled but the data was not successfully transferred to SD card, *writeEEPROMtoExternal()* is called and an attempt is made to write the entirety of the EEPROM to SD card. If this fails, the clinician can insert a new SD card and attempt to recover the DATA again.

If “intermediateDumpFail” indicates that the data dump following the EEPROM running out of capacity was either never attempted (as the EEPROM never ran out of capacity) or never failed, then the current “EEPROMAddress” is compared to the “minEEPROMAddress”. If these values are not the same, then there is data in the EEPROM.

- *writeEEPROMtoExternal()* is called and an attempt is made to write the data to SD card.
- *writeEEPROMtoExternal()* returns a 1 if the attempt was successful, or returns a 2 if the write failed.

If *writeEEPROMtoExternal()* returned a 1:

- EEPROM address 00 and address 01 (the address multiplier and the address offset) are set to their minimum values.
- “EEPROMAddress” is set to “minEEPROMAddress”

22.2.1.10 *void sleepNow()*

This function takes no inputs and returns nothing. It enables Interrupt 0 (which is on digital pin 2) and sets it to interrupt when this port experiences any change from HIGH to LOW or LOW to HIGH. The board is put into sleep mode using the LowPower library designed by Rocket Scream. With this call, the analogue to digital converter is switched off but brownout detection is left on.

Please note that the *avr/sleep* library is also in use. The *sleep_enable()* function of this library enables the sleep bit in the MCU control register.

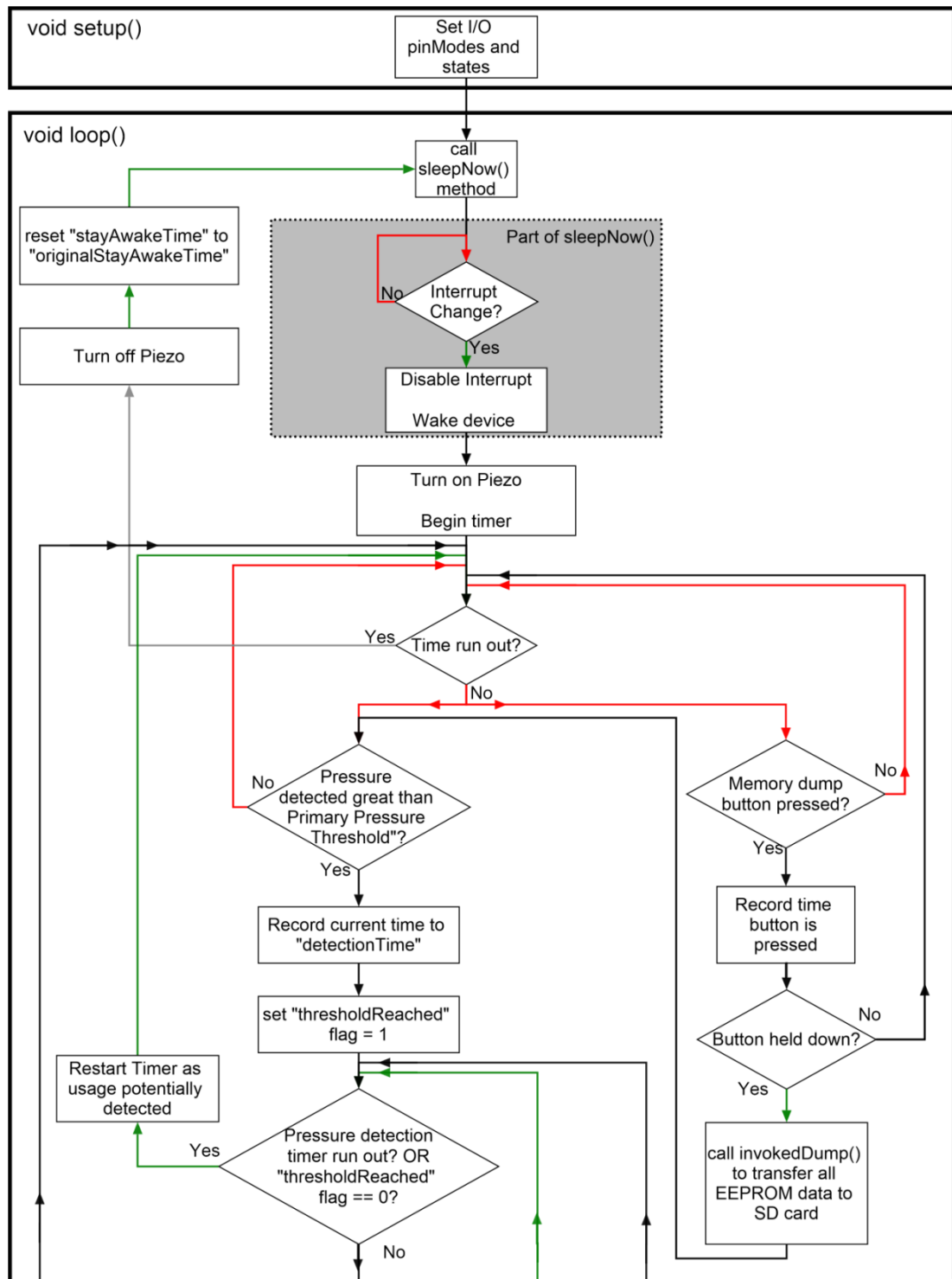
When the board wakes, the function *wake()* is called. When the device wakes, Interrupt 0 is disabled.

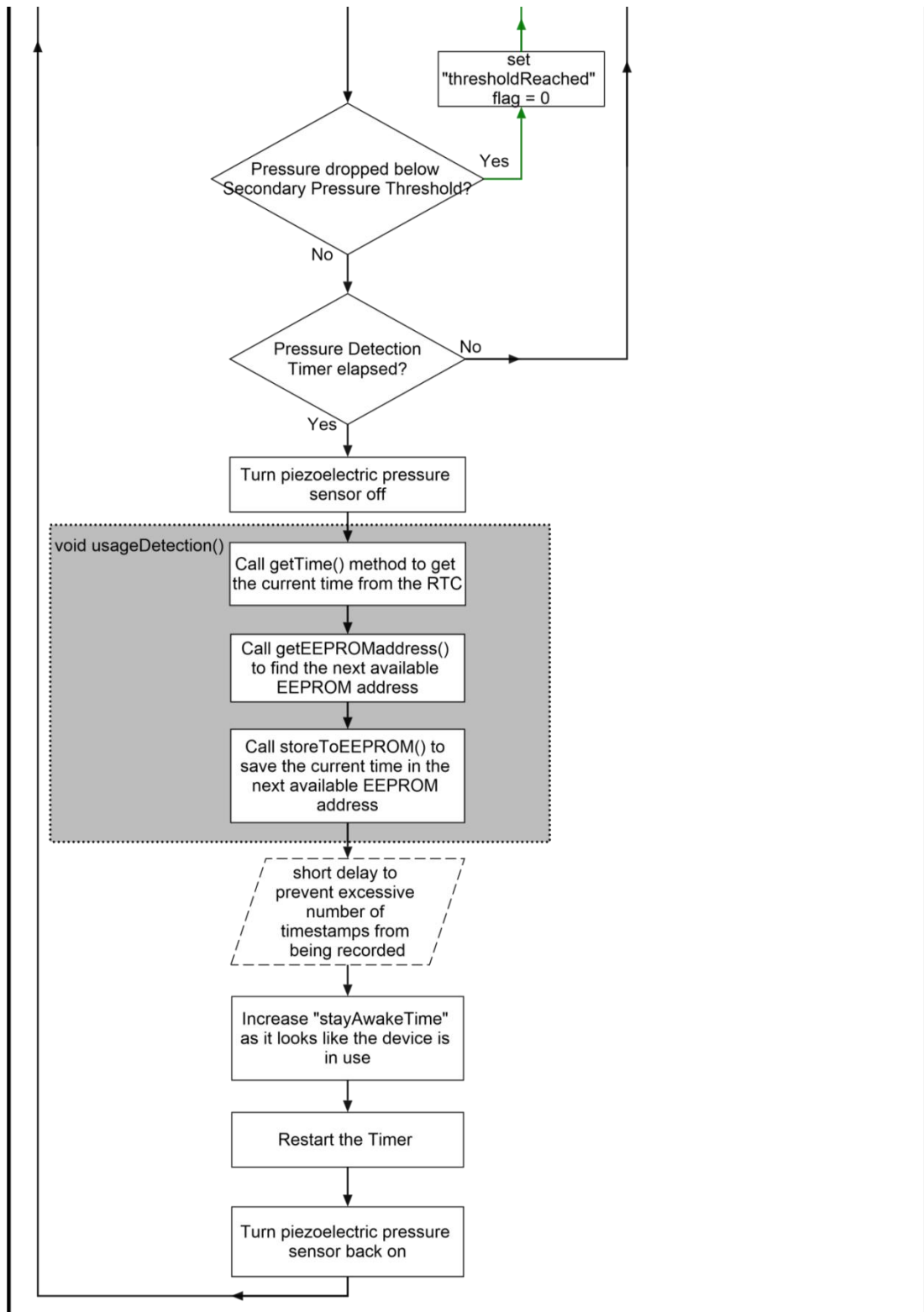
22.2.1.11 *void wake()*

This function takes no inputs and returns nothing. This is the function that is called by the interrupt. It calls the *sleep_disable()*, which is a function of the *avr/sleep* library.

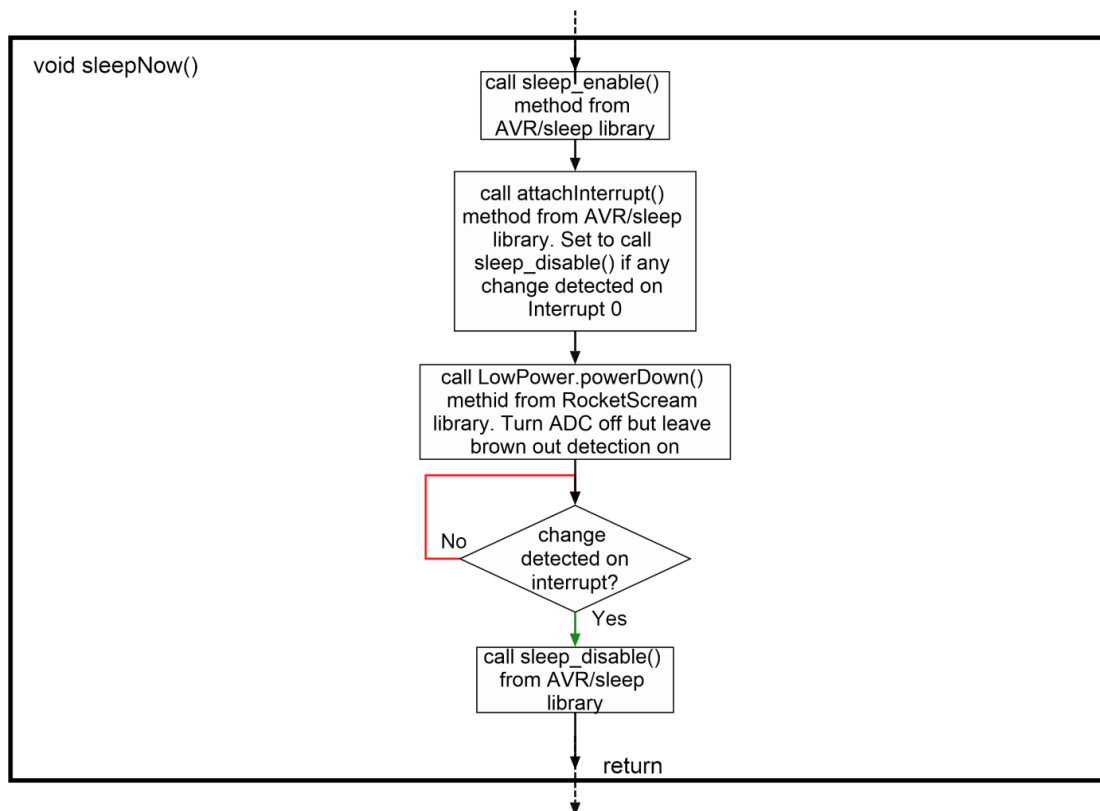
Algorithm Flow Charts

23.1.1.1 *void setup()* and *void loop()*

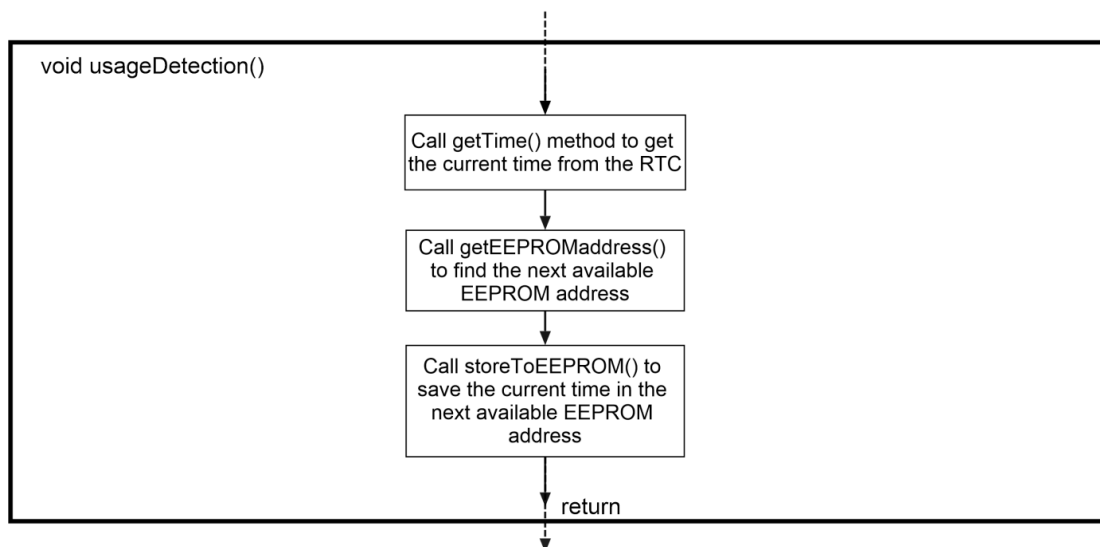




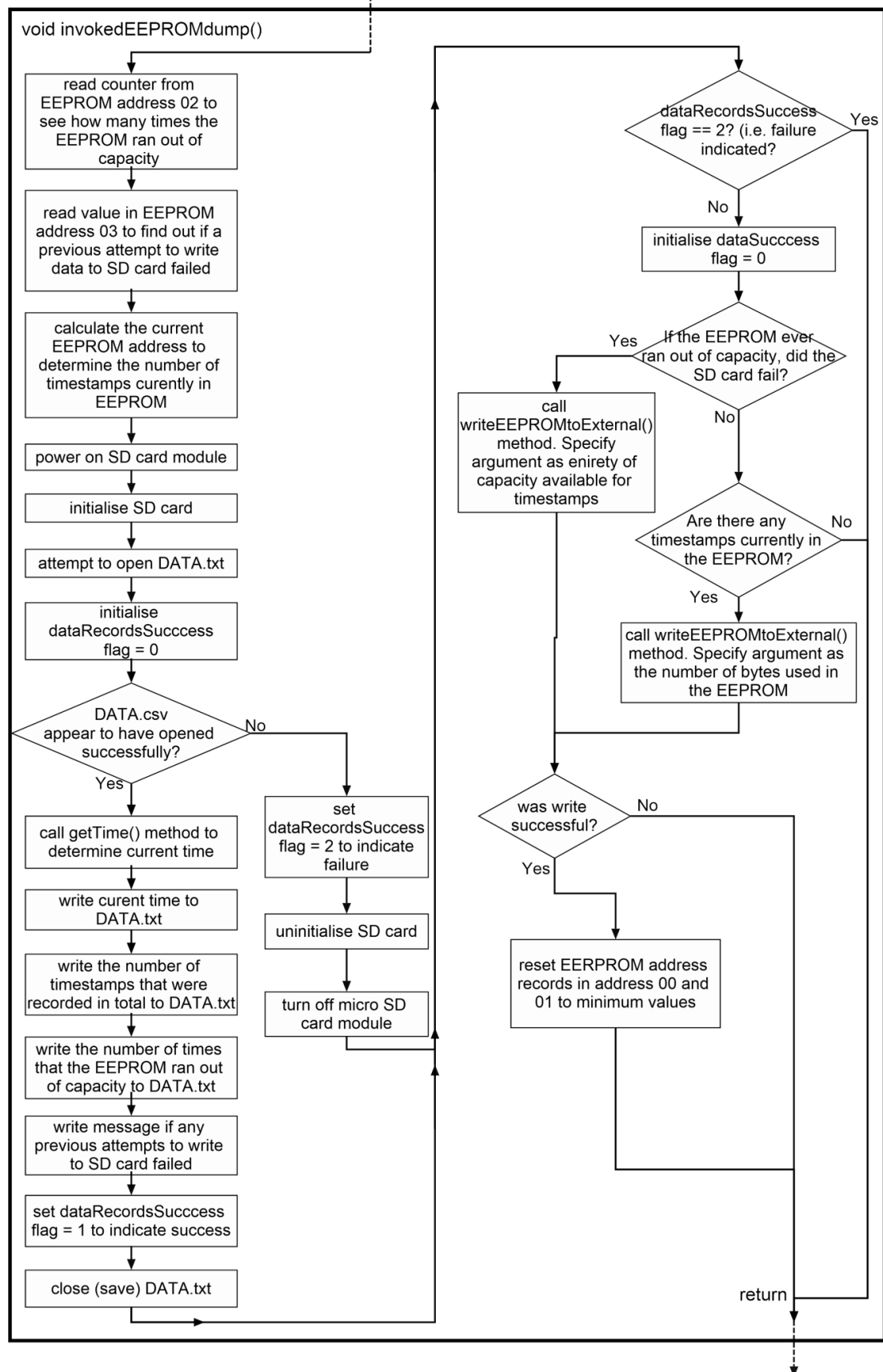
23.1.1.2 *void sleepNow()*



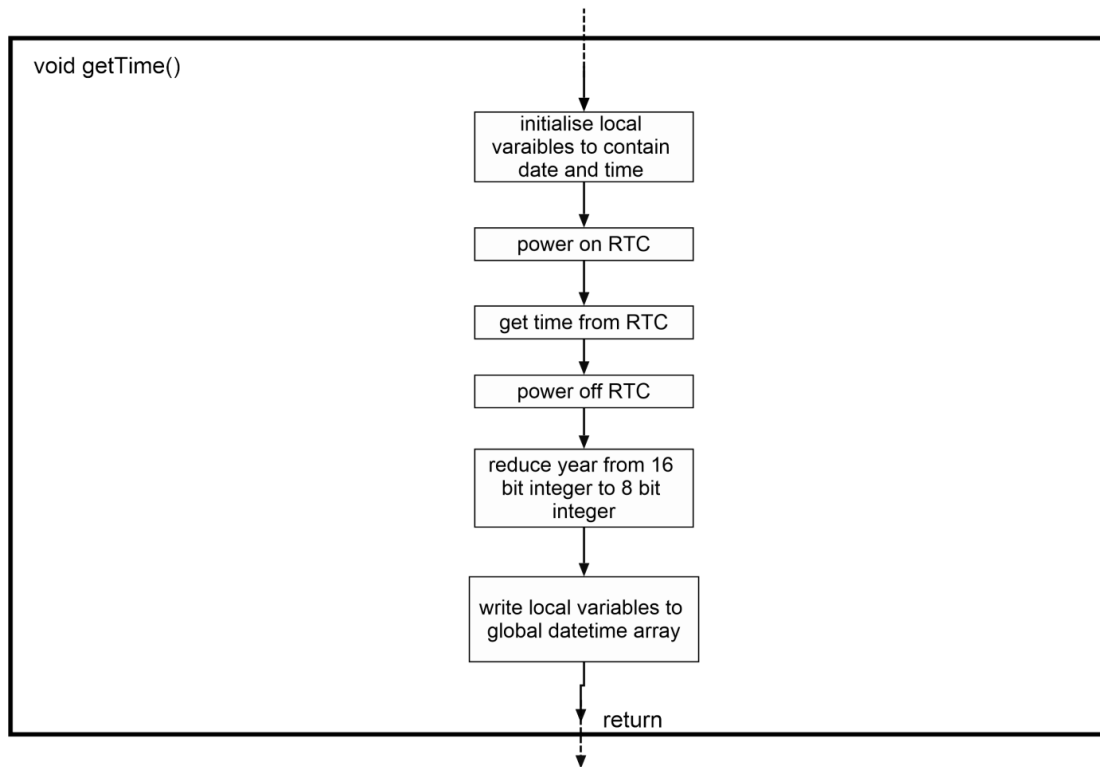
23.1.1.3 *void usageDetection()*



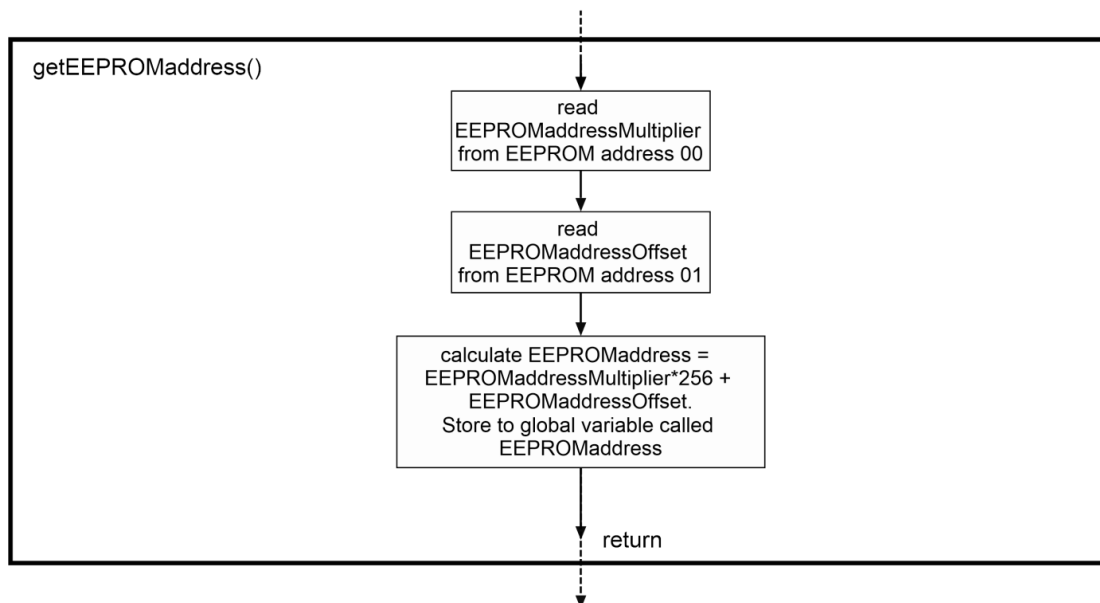
void invokedEEPROMdump()



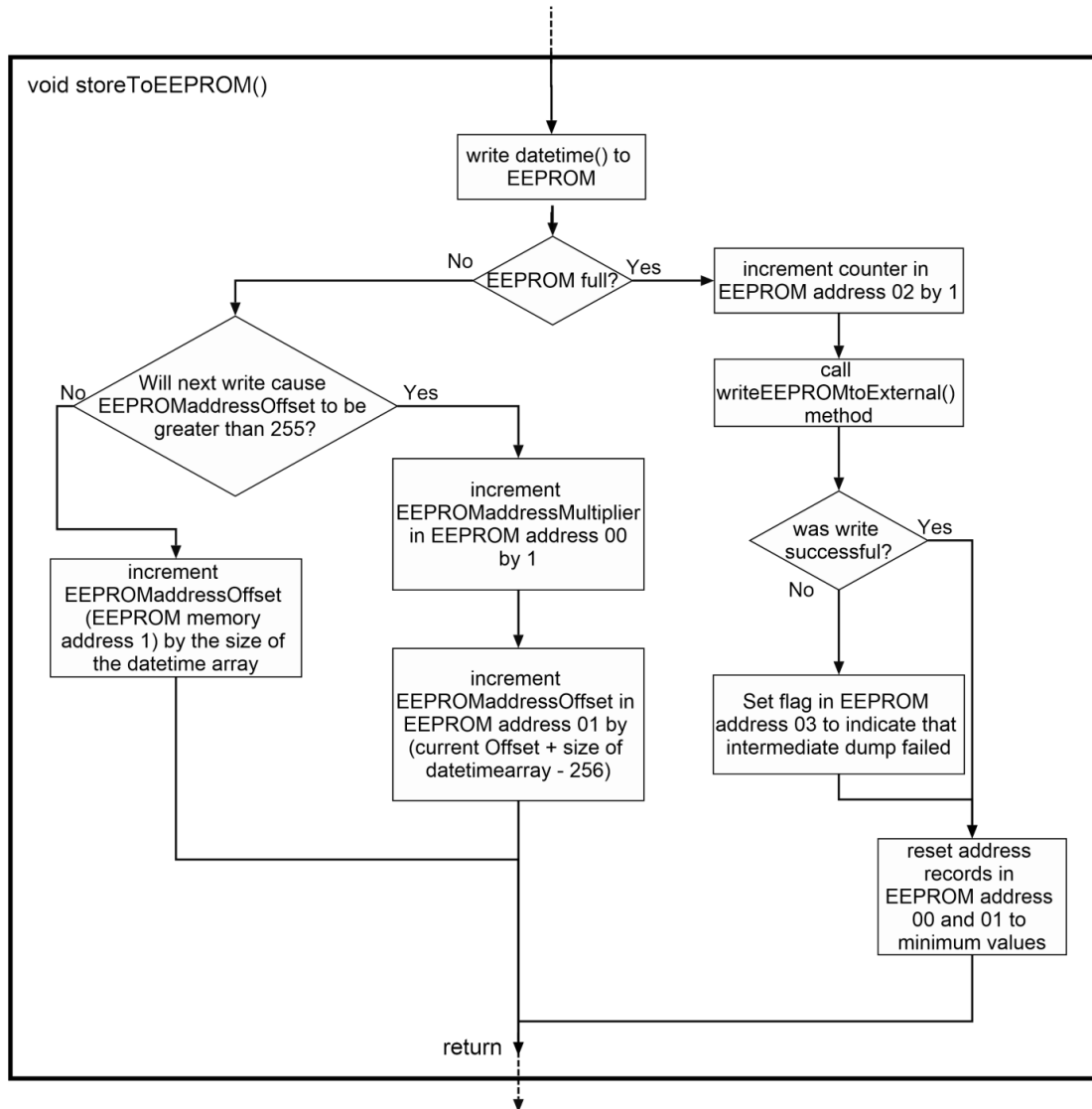
23.1.1.4 *void getTime()*



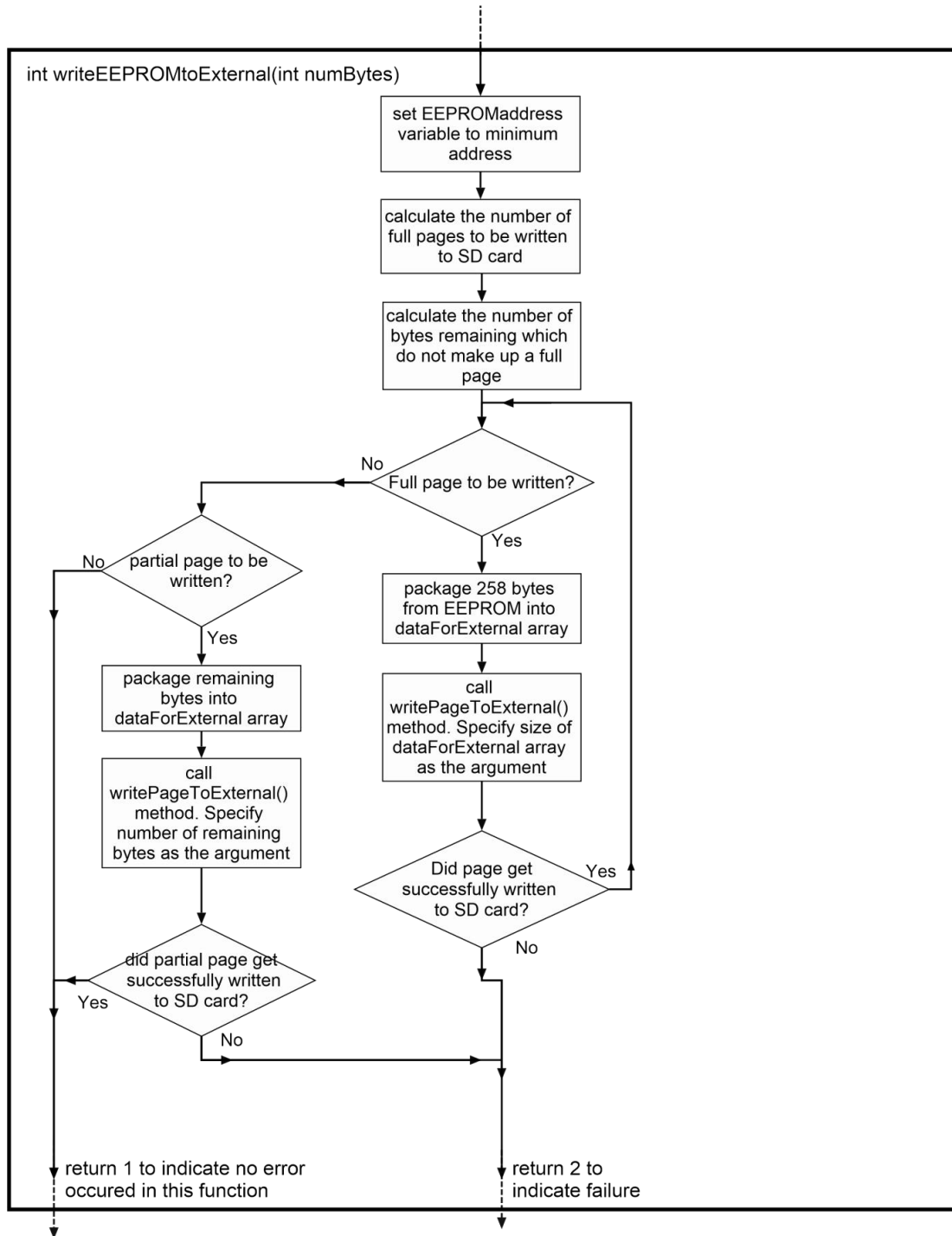
23.1.1.5 *void getEEPROMAddress()*



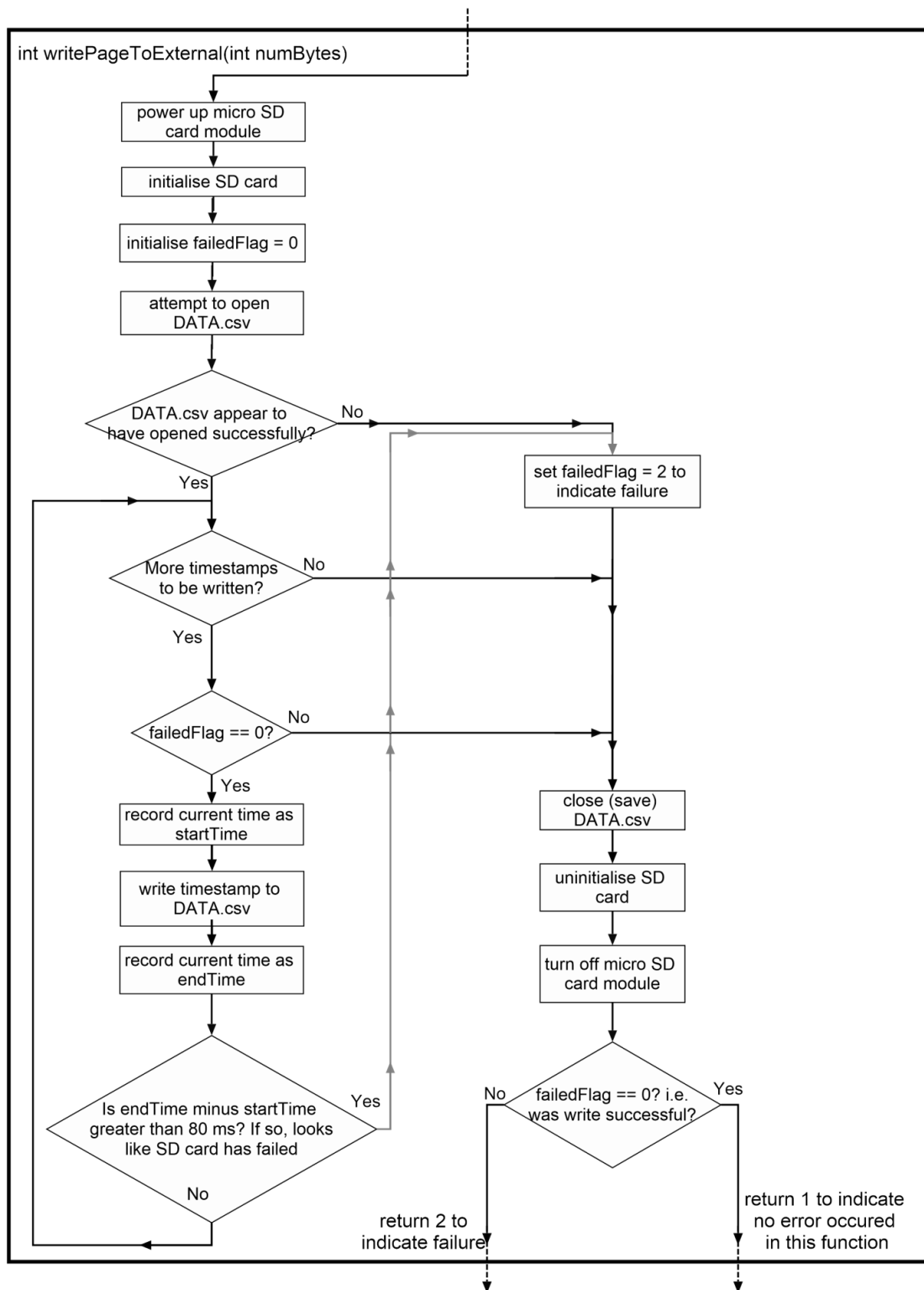
23.1.1.6 *void storeToEEPROM()*



23.1.1.7 *int writeEEPROMtoExternal(int numBytes)*



23.1.1.8 *int writePageToExternal(int numBytes)*



Arduino Code

```
/*
*****
* Killian Haycock
* Date: 09-May-2016
* Adherence Device Firmware - Including Debug Functionality.
*
* EEPROM address 00 and 01: Address records
*
* EEPROM address 02: Counter for number of times EEPROM has run out of capacity
*
* EEPROM address 03:
*   0 = no errors
*   1 = memory filled and intermediate dump failed
*   2 = debug failed only
*   3 = intermediate dump failed and debug failed
*****
*/

#include <SD.h>          //modified using http://forum.arduino.cc/index.php?topic=60513.0
#include <avr/sleep.h>    //Atmel AVR sleep and power management library
#include <LowPower.h>     //RocketScream Library
#include <EEPROM.h>       //EEPROM handling library
#include <Wire.h>         //Wire library
#include <RV8523.h>       //RTC library
#include <SPI.h>          //Serial Peripheral Interface library
RV8523 rtc;

/** Pin assignments *****/
const int piezo PROGMEM = A0; // analogue signal from piezoelectric pressure sensor
const int writeToExternal PROGMEM = 3; // physically submerged button used invoke the
movement of data from EEPROM to external memory.
const int LED PROGMEM = 13; // LED on development board. Will be removed for final
version. Good for tests/debugging
const int piezoPower PROGMEM = 7; // digital pin that controls power to the piezoelectric
pressure sensor
const int RTCpower PROGMEM = 8; // digital pin that controls power to the RTC
const int externalMemoryPower PROGMEM = 9; // digital pin that controls power to the
external memory module
/**/

/** User defined variables *****/
const int buttonHoldTime PROGMEM = 1000; // User defined: Time that "writeToExternal"
button must be held down for in order to envoke a dump of EEPROM to external memory.
const unsigned long originalStayAwakeTime PROGMEM = 3000; // User defined: number of
milliseconds that device will stay awake for.
unsigned long stayAwakeAfterDetection = 30000; // User defined: number of milliseconds
that device will stay awake for after the first detection. A detection means that the apparatus
is being used.
int primaryPressureThreshold = 220; // User defined: sensitivity of the piezoelectric
pressure sensor. Lower = more sensitive
int secondaryPressureThreshold = 208; // User defined: sensitivity of the piezoelectric
pressure sensor during the interval after Primary Pressure Threshold exceeded.
const unsigned long usageDetectionInterval PROGMEM = 700; // when pressure switch is
activated, record one time/date and delay for this time interval.
const unsigned long pressureDetectedTimer PROGMEM = 600; // when pressure switch is
activated,monitor it for this amount of time. If the pressure switch remains active for this
amount of time, device is in use.
/**/
```

```

/** System variables *****/
uint8_t datetime[] = {0, 0, 0, 0, 0, 0} ; //DDMMYYHHMMSS. Array to contain the date and
time obtained from the RTC.
byte dataForExternal[258]; //43 6-byte date/time records. Array of contiguous block of bytes
that can be written to the external memory
unsigned long buttonChangeTime = millis(); // variable used to store the time at which the
"writeToExternal" button is pressed.
byte lastButtonState = LOW;
//int dumpSuccess = 0; // variable used to flag if the write to external was successful or
failed. 0 == reset. 1 == success. 2 == failed.
unsigned long stayAwakeTimerBegin = 0; // variable to contain millis() when the device
wakes up.
unsigned long stayAwakeTime = originalStayAwakeTime; // integer that should not be
modified! Variable used to change the length of time that the device will stay awake for.
int EEPROMAddress; // variable used to hold the EEPROM address that is currently being
accessed.
int EEPROMAddressMultiplier; // this will be read from and written to EEPROM address 0.
Used to calculate the EEPROM address that the next date/time stamp should be written to.
Will be used by several functions.
int EEPROMAddressOffset; // this will be read from and written to EEPROM address 1.
Used to calculate the EEPROM address that the next date/time stamp should be written to.
Will be used by several functions.
int minEEPROMAddress = 4; // lowest EEPROM address that date/time data can be stored
to. Lower addresses are reserved for other purposes.
int maxEEPROMAddress; // will be stored when memory is full. Will only be needed if
memory dump has failed.
/*****/

```

```

void setup(){
  pinMode(externalMemoryPower, OUTPUT);
  digitalWrite(externalMemoryPower, LOW);
  pinMode(RTCpower, OUTPUT);
  digitalWrite(RTCpower, LOW);
  pinMode(piezoPower, OUTPUT);
  digitalWrite(piezoPower, LOW);
  pinMode(LED, OUTPUT);
  digitalWrite(LED, LOW);
  pinMode(piezo, INPUT);
  pinMode(writeToExternal, INPUT);

  debugSDwrite("***"); //DEBUG: indicate that device started/recovered from brown-out
}

```

```

void loop()
{
  sleepNow(); //run sleep function. Puts device to sleep.
  debugSDwrite("W"); //DEBUG: indicate that the device woke up
  int i;
  for (i = 0; i < 3; i++){
    digitalWrite(LED, HIGH); //DEBUG: flash LED to indicate movement detected
    delay(10);
    digitalWrite(LED, LOW);
    delay(10);
  }
  stayAwakeTimerBegin = millis(); // record current time for countdown timer
  digitalWrite(piezoPower, HIGH); // switch on piezoelectric pressure sensor
  delay(30); // 5 milliseconds required for piezo power-up to data ready according to
Honeywell SSC Series data sheet. However, 6ms was too short. 30ms appears to be
adequate.
}

```

```

    while ((millis() - stayAwakeTimerBegin) <= stayAwakeTime){ //loop until "stayAwakeTime"
has elapsed. "stayAwakeTime" value becomes longer after pressure is detected. Initially, it
is short.
        int pressureReading = analogRead(piezo); // get analogue reading from piezoelectric
pressure sensor.
        int memoryButtonState = digitalRead(writeToExternal); //check state of button that writes
contents of EEPROM to external memory

        if ((memoryButtonState != lastButtonState)){ // if the button state has changed. Debounce.
buttonChangeTime will settle when button stops changing
            buttonChangeTime = millis(); // reset the timer
            debugSDwrite("B"); //DEBUG: indicate that the button was pressed. Track any
accidental button presses.
        }

        if ((memoryButtonState == HIGH) && ((millis() - buttonChangeTime) > buttonHoldTime)){
// if the state of the button is high (pressed) and the button has been pressed for longer than
the user defined "buttonHoldTime"
            debugSDwrite("I"); //DEBUG: indicate the button has been held down and the
invokedEEPROMdump function is being called.
            invokedEEPROMdump(); // run function that will check to see if there is any data in the
internal EEPROM and will write any data to external memory
            memoryButtonState = LOW; // set low for reset.
        }
        lastButtonState = memoryButtonState; // record button state for next loop

        if (pressureReading >= primaryPressureThreshold){ // if the piezoelectric pressure sensor
has detected a pressure greater than the empirically found value.
            unsigned long detectionTime = millis(); // record time threshold pressure was reached
            byte thresholdReached = 1;
            debugSDwrite("PD"); //DEBUG: indicate that the piezoelectric pressure sensor has
detected some pressure greater than the primaryPressureThreshold

            while (((millis() - detectionTime) <= pressureDetectedTimer) && thresholdReached ==
1){
                delay(1); //delay is required here. The following pressure reading gets misrepresented
without this delay.
                pressureReading = analogRead(piezo);
                if (pressureReading < secondaryPressureThreshold){ // if pressure dropped below the
secondaryPressureThreshold before the timer elapsed
                    String timeout = String(millis() - detectionTime, DEC); // DEBUG: track how long
pressure was detected for
                    char charTimeout[4]; // DEBUG: create char
                    timeout.toCharArray(charTimeout, 4); // DEBUG: convert time to char
                    debugSDwrite(charTimeout); // DEBUG: write string containing number of
milliseconds that pressure was detected for
                    thresholdReached = 0; //lower flag
                }
            }

            stayAwakeTimerBegin = millis(); // restart counter.

            if (thresholdReached == 1){ // timeout. If pressure was consistantly high:
                digitalWrite(piezoPower, LOW); // we can turn off the piezo for the duration of the next
function.
                debugSDwrite("U"); // DEBUG: Indicate that a potential usage has been detected
                usageDetection(); // run the function that will get the current time from the RTC,
determine where to store it to the EEPROM, and actually store it to the EEPROM.
                delay(usageDetectionInterval); // delay to prevent excessive number of timestamps
from being recorded.

```

```

        stayAwakeTime = stayAwakeAfterDetection; // if pressure detected, increase timer so
device will stay awake.
        stayAwakeTimerBegin = millis(); // reset timer. This will prolong the time spent in the
while loop that is in the loop() function.
        digitalWrite(piezoPower, HIGH); // turn the piezoelectric pressure sensor back on.
        delay(30); // time for piezo to reinitialise
    }
}
}
stayAwakeTime = originalStayAwakeTime; // reset to short timeout after final detection
debugSDwrite("TO"); // DEBUG: indicate that the timer has elapsed and the device is
about to go ack to sleep
digitalWrite(piezoPower, LOW); // switch off the piezoelectric pressure sensor
}

```

```

void sleepNow(){ //Function that actually puts the development board to sleep.
    sleep_enable (); // enables the sleep bit in the MCU control register. This is part of the
"avr/sleep" library
    attachInterrupt (0, wake, CHANGE); // wake on any change to digital I/O 2 (interrupt 0)
    LowPower.powerDown(SLEEP_FOREVER, ADC_OFF, BOD_ON); // sleep using Rocket
Scream's library
    detachInterrupt (0); // stop interrupt
}

```

```

void wake(){ //Function that is run as soon as device wakes up.
    sleep_disable(); // This function is part of the "avr/sleep" library. Unfortunately this cannot
be directly seen by attachInterrupt() in sleepNow().
}

```

```

void usageDetection(){ // Function that is run when the piezoelectric pressure sensor detects
a value above the empirically determined value. Gets the current time from the RTC,
determines where to store it to EEPROM, and stores it to EEPROM.
    int i;
    for (i = 0; i < 3; i++){
        digitalWrite(LED, HIGH); //DEBUG: flash LED to indicate pressure has been detected
        delay(10);
        digitalWrite(LED, LOW);
        delay(10);
    }
    getTime(); // get the time from the RTC
    getEEPROMaddress(); // determine the next free EEPROM address
    storeToEEPROM(); // store the date and time to EEPROM
}

```

```

void invokedEEPROMdump(){ // Function that will determine if there are any date/time
records in the EEPROM and will attempt to write these to microSD card.
    int numDumps = EEPROM.read(2); // get the number of times that the EEPROM ran out of
capacity.
    int intermediateDumpFail = EEPROM.read(3); // find out if capacity was filled and card write
failed. DEBUG: also find out if sd card failed during debug function call
    getEEPROMaddress(); // determine the number of records currently in EEPROM memory.
    File dataRecordsFile;
    digitalWrite(externalMemoryPower, HIGH); // Switch on the SD card
    delay(100); // delay for stability
    SD.begin(10); // initialise the SD card
    delay(100); // delay for stability
    dataRecordsFile = SD.open("DATA.txt", FILE_WRITE); // open the text file "DATA.txt".
    int dataRecordsSuccess = 0;

    if (dataRecordsFile){ // if the file opened successfully

```

```

    dataRecordsFile.print(F("Current date/time: "));
    getTime();
    int i;
    for (i = 0; i < sizeof(datetime); i++){ // for each element of that date/time record:
        if (datetime[i] < 10){ // if the number is less than 10, add a leading 0 in the CSV file. This
looks better.
            dataRecordsFile.print(F("0"));
        }
        if (i < 2){ // if we are looking at the Day or Month, print and follow with "/"
            dataRecordsFile.print(datetime[i], DEC); // Day, Month
            dataRecordsFile.print(F("/"));
        }
        if (i == 2){ // if we are looking at the Year, print and follow with CVS delimiter ","
            dataRecordsFile.print(datetime[i], DEC); // Year
            dataRecordsFile.print(F("\t"));
        }
        if (i > 2 && i < 5){ // if we are looking at the Hour or Minute, print and follow with ":"
            dataRecordsFile.print(datetime[i], DEC); // Hour, Min
            dataRecordsFile.print(F(":"));
        }
        if (i == 5){ // if we are looking at the second, print and print new line feed into file
            dataRecordsFile.println(datetime[i], DEC); // second
        }
    }

    dataRecordsFile.print(F("Total number of Date/Time stamps: ")); // calculate the total
number of date/time stamps that were recorded. Print results to file.
    dataRecordsFile.println((170 * numDumps) + (EEPROMAddress - minEEPROMAddress) /
6);
    dataRecordsFile.print(F("The EEPROM memory was filled "));
    dataRecordsFile.print(numDumps);
    dataRecordsFile.println(F(" time(s)."));
    dataRecordsFile.println(F(""));

    switch (intermediateDumpFail){
        case 1:
            dataRecordsFile.print(F("Intermediate dump failed."));
            break;

        case 2: dataRecordsFile.print(F("Debug failed but intermediate dump never attempted or
never failed."));
            break;

        case 3: dataRecordsFile.print(F("Intermediate dump failed and debug failed."));
            break;
    }
    dataRecordsSuccess = 1;
    dataRecordsFile.close(); // close the file so that changes are made to the file.
}

else { // if file did not open.
    dataRecordsSuccess = 2;
}

SD.stop(); // uninitialise the SD card.
digitalWrite(externalMemoryPower, LOW); // switch off SD card power

if (dataRecordsSuccess == 2){
    return; // if SD write failed, do not try to write data.
}

else {

```

```

    debugSDwrite("S1"); //DEBUG: indicate that DATA.txt was successfully written to SD card
    int dataSuccess = 0;
    if ((intermediateDumpFail == 1) || (intermediateDumpFail == 3)){ // 1: intermediate dump
failed. 2: debug write failed. 3: both intermediate dump and debug failed
        dataSuccess = writeEEPROMtoExternal(maxEEPROMAddress - minEEPROMAddress);
//write all to SD card
    }
    else { // if intermediate dumps did not fail or were not attempted
        if (EEPROMAddress != minEEPROMAddress){ //if there is something to write to external
memory
            dataSuccess = writeEEPROMtoExternal(EEPROMAddress - minEEPROMAddress); //
call function to write data to external memory. Pass in the number of bytes that need to be
written.
        }
    }

    if (dataSuccess == 1){
        EEPROM.write(0, 0); // write EEPROM multiplier to 0
        EEPROM.write(1, minEEPROMAddress); // write EEPROM address offset to lowest
non-reserved address.
        EEPROMAddress = minEEPROMAddress; // reset the current address being used to the
minimum address. Only required here if device is going to be reused again instantly after
memory dump.
        debugSDwrite("S2"); //DEBUG: indicate that DATA.csv was successfully
written/appended
    }
    else {
        int i;
        for (i = 0; i < 5; i++) { // flash LED to indicate invokedDump() failed.
            digitalWrite(LED, HIGH);
            delay(1000);
            digitalWrite(LED, LOW);
            delay(1000);
        }
        return;
    }
}

int i;
for (i = 0; i < 6; i++) { // flash LED if successful.
    digitalWrite(LED, HIGH);
    delay(500);
    digitalWrite(LED, LOW);
    delay(500);
}
}

```

```

void getTime() { // Function to get the current time and date from the RTC
    uint8_t sec, min, hour, day, month;
    uint16_t year; // valid up to 2255. Year will store as "100" in 2100. We do not expect device
to be in operation beyond 2099. We treat year as 8-bit value to maximize memory utilisation.
    digitalWrite(RTCpower, HIGH); // switch on the RTC
    delay(20); //Appears to require at least 5ms.
    rtc.get(&sec, &min, &hour, &day, &month, &year); // get values from RTC.
    digitalWrite(RTCpower, LOW); // Switch off the RTC
    uint8_t yearByte = year - 2000; // decrease by 2000 to produce 3-digit value. Cast to 8-bit
integer

    datetime[0] = day; // store values into array.
    datetime[1] = month;
    datetime[2] = yearByte;
}

```

```

    datetime[3] = hour;
    datetime[4] = min;
    datetime[5] = sec;
}

```

```

void getEEPROMAddress() { // read EEPROM addresses 0 and 1 and calculate the next
available EEPROM address.

```

```

    EEPROMAddressMultiplier = EEPROM.read(0); // read EEPROM addresses 0 and 1
    EEPROMAddressOffset = EEPROM.read(1);
    EEPROMAddress = EEPROMAddressMultiplier * 256 + EEPROMAddressOffset; //
Calculate EEPROM address: 256 multiplied by value in address 0 will equal 0, 256, 512, or
768. Add some value between 0 and 255 (byte_offset) to determine exact address
}

```

```

void storeToEEPROM() { // Function that will write the date/time array to EEPROM. Update
EEPROM memory address records only after data has been written
// See device documentation for explanation of this function.

```

```

    int i;
    for (i = 0; i < sizeof(datetime); i++){ // for each element of the "datetime" array.
        EEPROM.write(EEPROMAddress, datetime[i]); // write element of array to current
"EEPROMAddress"
        EEPROMAddress++; // increment "EEPROMAddress"
    }

```

```

    if (EEPROMAddress > 1018) { // 1023 - 5 = 1018. This is the last possible EEPROM
memory address that the 6-element date/time array can be stored to. Anything greater than
1018 will cause the latter elements to overwrite the first addresses.

```

```

        debugSDwrite("EF"); //DEBUG: indicate that the EEPROM has run out of capacity.
        int numDumps = EEPROM.read(2); // number of times EEPROM ran out of capacity.
        EEPROM.write(2, numDumps + 1); // Update record of number of times EEPROM ran out
of capacity.

```

```

        maxEEPROMAddress = EEPROMAddress; // record for invoked dump at a later stage.
        int success = writeEEPROMtoExternal(EEPROMAddress - minEEPROMAddress); //write
all bytes that contain date/time records. The actual number of bytes is a multiple of the size
of the date/time records. We can use the current calculated address, minus the reserved
bytes, to determine the number of bytes. The reserved bytes are used to record EEPROM
addresses.

```

```

        if (success == 2){ //if dump failed
            int failState = EEPROM.read(3);
            switch (failState) {
                case 0:
                    EEPROM.write(3, 1); // EEPROM capacity full and dump failed
                    break;

                case 2:
                    EEPROM.write(3, 3); // EEPROM capacity full and dump failed and debug previously
failed
                    break;
            }
        }
}

```

```

        EEPROM.write(0, 0); // reset EEPROM address records to minimum values
        EEPROM.write(1, minEEPROMAddress); // reset EEPROM address records to minimum
values
    }

```

```

    else if ((EEPROMAddressOffset + sizeof(datetime)) > 255) { // if next date/time record will
cause an overflow in the "EEPROMAddressOffset" memory record byte

```

```

        EEPROM.write(0, EEPROMAddressMultiplier + 1); // update the
"EEPROMAddressMultiplier" byte stored in address 0.

```

```

    EEPROM.write(1, (EEPROMAddressOffset + sizeof(datetime) - 256)); // update the
    "EEPROMAddressOffset" byte.
}

else {
    EEPROM.write(1, (EEPROMAddressOffset + sizeof(datetime))); // Otherwise, just update
    the "EEPROMAddressOffset" by 6.
}
}

```

int writeEEPROMtoExternal(int numBytes){ // Function that packages date/time records that are in the EEPROM into pages, and calls the function that will write each page to microSD card when a page is populated. The number of bytes that need to be moved to microSD card is passed into this function. Number of pages that are required is calculated from this. //Buffers up to 258 bytes into a page. Writes page to external memory device and repeats until all EEPROM data is transferred.

EEPROMAddress = minEEPROMAddress; // set current address to minimum possible address.

int numPages = numBytes / sizeof(dataForExternal); // calculate and keep truncated value. This is the number of full pages required

int overflowBytes = numBytes - (numPages * sizeof(dataForExternal)); // remaining bytes (partial page)

int numRecords = numBytes / sizeof(datetime); // only calculated for display. Can be removed in final version

int j;

for (j = 0; j < numPages; j++){ // for each of the full pages

int i;

for (i = 0; i < sizeof(dataForExternal); i++){ //buffer contiguous blocks of full buffer size

dataForExternal[i] = EEPROM.read(EEPROMAddress); // take a value from current EEPROM address and place into the ith element of the "dataForExternal" array

EEPROMAddress++; // increment current EEPROM address

}

int pageSuccess = writePageToExternal(sizeof(dataForExternal)); // call writePageToExternal() function. Include number of bytes to be written in the call. In this case, for full pages, the number of bytes is always the same.

if (pageSuccess == 2){ //if page write failed
return 2;

}

}

if (overflowBytes != 0) //if there are some excess bytes (i.e. a partial page is required)

{

int i;

for (i = 0; i < overflowBytes; i++){ // for each of the excess bytes

dataForExternal[i] = EEPROM.read(EEPROMAddress); // take a value from the current EEPROM address and place into the ith element of the "dataForExternal" array

EEPROMAddress++; // increment current EEPROM address

}

int pageSuccess = writePageToExternal(overflowBytes); // call writePageToExternal() function. include number of bytes to be written in the call. In this case, number of bytes is equal to the number of excess bytes.

if (pageSuccess == 2){ //if page write failed
return 2;

}

}

debugSDwrite("WS"); // DEBUG: indicate writeEEPROMtoExternal() was successful
return 1; //if completed this ftn without any errors, return 1.


```
}
```

```
int writePageToExternal(int numBytes){ // This function writes the buffered page of date/time records to microSD card. Records are written to a file called "DATA.csv". Records are formatted into a presentable format.
```

```
// However, "dataFile" always becomes 1 if the file is re-opened after an initial successful opening. It becomes 1 then even when the SD card has been physically removed from the device. It returns 0 after closed, but always re-returns 1 when an attempt is made to re-open the file.
```

```
File dataFile;  
digitalWrite(externalMemoryPower, HIGH); // switch on the microSD card.  
delay(100); // delay to ensure stability  
SD.begin(10); // initialise the SD card  
delay(100); // delay to ensure stability  
int failedFlag = 0;  
int k; // initialise dummy variable for loops
```

```
dataFile = SD.open("DATA.csv", FILE_WRITE); // open "DATA.csv" for writing
```

```
if (dataFile){ // if opened correctly (Bug: this always becomes 1 when an attempt is made to re-open a file that once opened successfully)
```

```
int i;  
for (i = 0 ; i < numBytes ; i = i + 6){ // take one 6-byte date/time record at a time  
if (failedFlag == 0){  
unsigned long startTime = millis();  
for (k = 0; k < sizeof(datetime); k++){ // for each element of that date/time record:
```

```
if (dataForExternal[k + i] < 10){ // if the number is less than 10, add a leading 0 in the CSV file. This looks better.
```

```
dataFile.print("0");
```

```
}
```

```
if (k < 2){ // if we are looking at the Day or Month, print and follow with "/"
```

```
dataFile.print(dataForExternal[k + i], DEC); // Day, Month
```

```
dataFile.print(F("/"));
```

```
}
```

```
if (k == 2){ // if we are looking at the Year, print and follow with CVS delimiter ","
```

```
dataFile.print(dataForExternal[k + i], DEC); // Year
```

```
dataFile.print(F(","));
```

```
}
```

```
if (k > 2 && k < 5){ // if we are looking at the Hour or Minute, print and follow with ":"
```

```
dataFile.print(dataForExternal[k + i], DEC); // Hour, Min
```

```
dataFile.print(F(":"));
```

```
}
```

```
if (k == 5){ // if we are looking at the second, print and print new line feed into file
```

```
dataFile.print(dataForExternal[k + i], DEC); // second
```

```
dataFile.print(F("\n")); // new row in CSV file
```

```
}
```

```
}
```

```
unsigned long endTime = millis();
```

```
if (endTime - startTime > 80){ // time taken to write each date/time stamp (6 bytes). If greater than 80ms, looks like a sd card failure. 80 empirically found to be good value.
```

```
failedFlag = 2; // DEBUG: set failedFlag here and uninitialise card immediately. Can't uninitialise and power down SD card at end of function when using debug code. The Debug function powers off sd card and so if this is not done here subsequent attempts to call SD.stop() cause the development board to hang
```

```
SD.stop(); // uninitialise the SD card. Must call here in Debug mode. Can be called later in function in final version
```

```
debugSDwrite("PF1"); // DEBUG: Indicate that SD card has failed here. If SD has failed, this message is not likely to be recorded.
```

```

    }
  } //end of "if failedFlag == 0"
}
} // end of "if (dataFile)"
else // if file did not open
{
  failedFlag = 2; // DEBUG: set failedFlag here and uninitialise card immediately. Can't
  uninitialise and power down SD card at end of function when using debug code. The Debug
  function powers off sd card and so if this is not done here subsequent attempts to call
  SD.stop() cause the development board to hang
  SD.stop(); // uninitialise the SD card. must call here in debug mode. can be called later in
  function in final version
  debugSDwrite("PF2"); // DEBUG: Indicate that SD card has failed here. If SD has failed,
  this message is not likely to be recorded
}
dataFile.close(); // close the file so that changes are made to the file.
//SD.stop(); // Uninitialise the SD card. DEBUG: Moved point at which this command is
called in debug version. Calling it here in debug version causes the developemtn board to
hang.
digitalWrite(externalMemoryPower, LOW); // switch off SD card power

if (failedFlag == 0){
  debugSDwrite("PS"); // DEBUG: Indicate that a page (or parital page) was successfully
  written to SD card.
  return 1; //if completed this ftn without any errors, return 1.
}

else { // failedFlag == 2;
  return 2;
}
}

```

void debugSDwrite(const char message[]){ // DEBUG function. Accepts short message.
Attempts to write short message to DEBUG.txt on the SD card.

```

  int currentState = EEPROM.read(3);
  if (currentState > 1){ //2 and 3 mean debug failed
    return;
  }

```

// If function did not return, intermediate dump never failed or never attempted, and debug
never attempted or never failed. Function will continue

```

  getTime();
  File dataFile_debug;
  digitalWrite(externalMemoryPower, HIGH); // switch on the microSD card.
  delay(100); // delay to ensure stability
  SD.begin(10); // initialise the SD card]
  delay(100); // delay to ensure stability
  int success = 0;
  unsigned long startTime = millis();
  dataFile_debug = SD.open("debug.txt", FILE_WRITE); // open "debug.txt" for writing
  int i; //dummy variable

```

```

  if (dataFile_debug){
    for (i = 0; i < sizeof(datetime); i++){ // for each element of that date/time record:
      if (datetime[i] < 10){ // if the number is less than 10, add a leading 0 in the CSV file. This
      looks better.
        dataFile_debug.print(F("0"));
      }
      if (i < 2){ // if we are looking at the Day or Month, print and follow with "/"
        dataFile_debug.print(datetime[i], DEC); // Day, Month
        dataFile_debug.print(F("/"));
      }
    }
  }

```

```

    }
    if (i == 2){ // if we are looking at the Year, print and follow with CVS delimiter ","
        dataFile_debug.print(datetime[i], DEC); // Year
        dataFile_debug.print(F("\t"));
    }
    if (i > 2 && i < 5){ // if we are looking at the Hour or Minute, print and follow with ":"
        dataFile_debug.print(datetime[i], DEC); // Hour, Min
        dataFile_debug.print(F(":"));
    }
    if (i == 5){ // if we are looking at the second, print and print new line feed into file
        dataFile_debug.print(datetime[i], DEC); // second
        dataFile_debug.print(F("\t")); // tab
    }
}

dataFile_debug.println(message);
unsigned long endTime = millis();

if (endTime - startTime > 80){ // If greater than 80ms, looks like a sd card failure. 80
    empirically found to be good value.
    success = 2;
}
}

else {
    success = 2;
}

dataFile_debug.close(); // close the file so that changes are made to the file.
SD.stop(); // uninitialise the SD card.
digitalWrite(memoryPower, LOW); // switch off SD card power

if (success == 2) {
    int failState = EEPROM.read(3);
    switch (failState) {
        case 0:
            EEPROM.write(3, 2); // Debug failed. Intermediate dump never attempted or never
            failed
            break;

        case 1:
            EEPROM.write(3, 3); // Debug failed and Intermediate dump failed
            break;
    }
}
}
}

```

Device Trials

Three people trialled the device using the *Debug* firmware. These trials exposed some of the issues with the device, and incrementally indicated modifications that ought to be made to the firmware.

For each trial, the clinician used the breath stacker in the same manner that a patient would. The engineer requested the user to record the times at which the breath stacker was used, and the duration of use. The user was also requested to record the times at which the breath stacker was moved.

Upon receiving the breath stacker back from the user, the engineer pressed the submerged button and invoked the movement of data from the internal EEPROM to the SD card. This caused the following files to be created on the micro SD card:

1. DATA.txt: Information file which specifies the number of timestamps recorded by the device, the time at which this file was created, the number of times that the internal EEPROM ran out of capacity, and specifies if the SD card ever failed.
2. DATA.csv: File created which contains a list of all the dates and times that a usage was detected by the device.
3. DEBUG.txt: This file is only created when the debug firmware is in use. This file contains additional information such as:
 - a. The date and time at which the device was moved (i.e. “woke”)
 - b. The date and time at which the device went back to sleep
 - c. The date and time at which the piezoelectric pressure sensor detected pressure above the pre-set threshold
 - d. The date and time at which a usage was detected (if the pressure remained sufficiently high for sufficiently long)
 - e. If a usage was not recorded after the piezoelectric sensor detected sufficient pressure, the time at which the pressure dropped and the duration of time that the piezoelectric pressure sensor detected pressure for is recorded
 - f. The date and time that the submerged button is pressed
 - g. The date and time that the submerged button is held down
 - h. The date and time that the device is powered on
 - i. The date and time when DATA.txt is written to the micro SD card
 - j. The date and time when a page of data (258 bytes or less) is written to DATA.csv
 - k. The date and time when DATA.csv is saved to micro SD card
 - l. The data and time that an attempt to write to microSD card failed

The user’s manual records were compared to the data obtained by the device.

The primary goals of these trials were to:

1. Expose any systemic or software bugs:
 - a. Verify that the device woke when the user claimed to have used the apparatus
 - b. Verify that the device detected usages when the user claimed to have used the apparatus

- c. Verify that the device **did not** detect usages when the user **did not** claim to have used the apparatus
 - d. Verify that the device did not wake on its own accord
 - e. Verify that the button was never activated at an unexpected time
 - f. Verify that an excessive number of timestamps are not being recorded each time the breath stacker is used
2. Indicate the amount of time that the device spent awake.

Trial 1: 02 October 2016 to 03 October 2016

No. of timestamps recorded by device in scope of trial	62
No. of timestamps which correspond to manual records	62
No. of timestamps which do not correspond to manual records	0
No. of timestamps which do not correspond to manual records and can be heuristically removed from records	n/a
Percentage of timestamps recorded by device which do not correspond to manual records	0%
Total duration of trial	25hr
Total time spent "awake"	0hr 11min 2sec
Time spent "awake" and not in use	0hr 0min 29sec

- No bugs were detected.
- Excellent correlation witnessed between the human usage records and the device records.
- No usages were detected at times other than those indicated by the user's manual records.
- The debug analysis indicates that the button was never pressed at unexpected times.

Trial 2: 21 October 2016 to 26 October 2016

No. of timestamps recorded by device in scope of trial	168
No. of timestamps which correspond to manual records	84
No. of timestamps which do not correspond to manual records	84
No. of timestamps which do not correspond to manual records and can be heuristically removed from records	83
Percentage of total timestamps which do not correspond to manual records	50%
Percentage of filtered timestamps which do not correspond to manual records	0.006%
Total duration of trial	6days 5hr 36min
Total time spent "awake"	0hr 38mins 13sec
Time spent "awake" and not in use	0hr 21mins 03sec

- Overall, the device appears to have operated as expected. Only one software bug was detected. Timestamp records had to be manually corrected as a result. The RTC library has since been updated and problem has not reoccurred since.
- Good correlation can be seen between the human usage records and the device records. The user admitted that the manual records were not extremely accurate.
- Facemask got compressed while in transit on one of the days during the trial. User was in transit for 2hrs 35mins. The mask was compressed for approximately 4 consecutive minutes. Analysis of DATA.csv alone indicates that these records are not detections of usage as each and every timestamp is precisely spaced for the entirety of the 4 minute window. Such records are extremely unlikely to have been created by normal use of the breath stacker apparatus.
- This trial highlighted the risk that the breath stacker might be in transit a great deal, and can easily become accidentally compressed and store incorrect data.
- Careful data analysis can indicate the times when timestamps were recorded but the breath stacker was not actually in use. When the apparatus is used correctly, a number of timestamps will be recorded. These are grouped together as breaths, inhalations and cycles.
 - A single, solitary, timestamp which is well spaced from any other timestamp indicates incorrect usage of the breath stacker apparatus or a spurious and erroneous detection of usage. These can easily be filtered out during data analysis.
 - An excessively period of constantly spaced timestamps indicates that the mask was compressed at a time when the apparatus was not in use. These erroneous records can be filtered out during data analysis.
- The debug analysis indicates that the button was never pressed at unexpected times.

Trial 3: 22 November 2016 to 25 November 2016

No. of timestamps recorded by device in scope of trial	106
No. of timestamps which correspond to manual records	100
No. of timestamps which do not correspond to manual records	6
No. of timestamps which do not correspond to manual records and can be heuristically removed from records	0
Percentage of total timestamps which do not correspond to manual records	0.057%
Percentage of filtered timestamps which do not correspond to manual records	0.057%
Total duration of trial	3days 5hr 33min
Total time spent “awake”	0hr 15mins 27sec
Time spent “awake” and not in use	0hr 12mins 18sec

- Overall, the device operated as expected. No firmware bugs were detected.
- Great correlation can be seen between the human usage records and the device records. In two instances during this trial, a usage timestamp was recorded by the device which did not correlate with the user’s manual records. In one of these instances, the user appears to have failed to manually record her activities. In the other instance, the facemask appears to have been accidentally compressed.
- This trial highlighted the amount of movement that the breath stacker might endure while with a patient.
- The debug analysis indicates that the button was never pressed at unexpected times.

Future Work

Thus far, the device appears to have excellent potential to track patient’s usage of the breath stacker apparatus. The scope of future work in this project is multifaceted.

Whilst the current firmware is functional, there are many improvements which ought to be made. There are an excessive number of hard coded values which need to be removed so that this firmware can become more generalised. Some of the current functions are clumsy in their operation, as is the algorithm in general. Some of the functions which currently exist do not need to reside as standalone functions and can be merged into other functions. The firmware should be improved so that it better suits the embedded environment in which it operates.

In terms of data processing, the standard firmware only collects the timestamps at which the apparatus is believed to be in use. Heuristic methods can be used to filter out any timestamps that are likely to have been erroneously collected; such as times when the mask was accidentally compressed. The debug firmware provides ample additional data that helps inform and guide these heuristic filtering decisions. The concept of collecting some of this additional data in the standard firmware

should be explored. While this is obviously possible to achieve in code, the overall effect on the longevity of the device would need to be analysed.

In terms of the hardware, research is required to find a potentially more suitable battery. The currently selected battery is physically quite large. The current RTC also appears to drift and so the extent and severity of this drift needs to be addressed. Research is also required to determine if a low-power wireless communications feature can be feasibly added to this device. Should this feature be considered, the clinician would need an intuitive method of interfacing with the device and retrieving the data. If this becomes possible in the future, then a hard mounted memory IC could also be implemented and the troublesome micro SD card and micro SD card module could be removed from the design.

We may consider designing a custom PCB to suit our needs. Such a custom design may be more stable, less fragile, and may consume less power than the current prototype. Issues such as the susceptibility of this device to water damage and the precarious nature of the micro SD card may need to be addressed. A more suitable, lower-power microcontroller may be considered. The unpleasant aesthetics of the device may also need to be reviewed.

Currently, we modify existing masks to accommodate the device. Glue is used in this process. The suitability and toxicity of this glue must be researched.

Additional and longer lasting trials are required to further test this device. Should further informal trials produce promising results, the device should be considered for clinical trials. The selection of the physical components would again need to be addressed in this respect.

Along with the need to collect sufficient statistical evidence to support the efficacy of this device, market research must also be carried out to determine the potential for this device. Uses in applications beyond motor neuron disease research must also be explored.

Should we deem this device to be patentable, our team must submit a patent application in the immediate future.

Appendix 13: Statistical Outputs

Appendix X: Statistics Outputs

Description of Study Group

	Distribution	Outliers	
Age	Normal	P:3	
Time from dx	Non parametric	4 x extreme	
		8 x outliers	
Age at diagnosis	Normal	2 x outliers	3, 25

Case Processing Summary

	Cases					
	Included		Excluded		Total	
	N	Percent	N	Percent	N	Percent
Age at study entry (years)	108	100.0%	0	0.0%	108	100.0%

Report

Age at study entry (years)

N	Mean	Std. Deviation
108	62.05	11.465

Case Processing Summary

	Cases					
	Included		Excluded		Total	
	N	Percent	N	Percent	N	Percent
AgeAtSymptomOnset	108	100.0%	0	0.0%	108	100.0%

Report

AgeAtSymptomOnset

N	Mean	Std. Deviation

108	59.0000	11.61453
-----	---------	----------

Report

AgeAtDiagnosis

N	Mean	Std. Deviation
108	60.1574	11.90787

Report

Time from diagnosis to study entry (months)

N	Median	Minimum	Maximum
108	8.50	0	90

Group Statistics

	Sex	N	Mean	Std. Deviation	Std. Error Mean
Age at study entry (years)	Female	37	65.43	9.921	1.631
	Male	71	60.28	11.878	1.410

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
									Lower	Upper
Age at study entry (years)	Equal variances assumed	1.314	.254	2.258	106	.026	5.151	2.281	.628	9.674
	Equal variances not assumed			2.389	85.376	.019	5.151	2.156	.865	9.437

Group Statistics

	Sex	N	Mean	Std. Deviation	Std. Error Mean
AgeAtDiagnosis	Female	37	62.4324	11.86391	1.95041
	Male	71	58.9718	11.84057	1.40522

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
									Lower	Upper
AgeAtDiagnosis	Equal variances assumed	.193	.661	1.440	106	.153	3.46060	2.40240	-1.30239	8.22359
	Equal variances not assumed			1.440	72.963	.154	3.46060	2.40390	-1.33041	8.25161

Ranks

	Sex	N	Mean Rank	Sum of Ranks
Time from diagnosis to study entry (months)	Female	37	56.97	2108.00
	Male	71	53.21	3778.00
	Total	108		

Test Statistics^a

	Time from diagnosis to study entry (months)
Mann-Whitney U	1222.000
Wilcoxon W	3778.000
Z	-.593
Asymp. Sig. (2-tailed)	.553

a. Grouping Variable: Sex

Case Processing

Summary

	Count
Overall	108
Excluded	0
Total	108

Ratio Statistics for Time from diagnosis to study entry (months) / Sex

Median	95% Confidence Interval for Median			Price Related Differential	Coefficient of Dispersion	Coefficient of Variation
	Lower Bound	Upper Bound	Actual Coverage			Median Centered
6.000	4.000	7.500	95.7%	1.106	1.363	228.6%

The confidence interval for the median is constructed without any distribution assumptions. The actual coverage level may be greater than the specified level.

Report

Time from diagnosis to study
entry (months)

Sex	N	Median
Female	37	10.00
Male	71	8.00
Total	108	8.50

Group Statistics

	Site of onset	N	Mean	Std. Deviation	Std. Error Mean
Age at study entry (years)	Spinal	85	62.22	11.705	1.270
	Bulbar	23	61.39	10.752	2.242

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
									Lower	Upper
Age at study entry (years)	Equal variances assumed	.036	.849	.308	106	.759	.832	2.706	-4.533	6.198
	Equal variances not assumed			.323	37.365	.748	.832	2.577	-4.387	6.051

Group Statistics

	Site of onset	N	Mean	Std. Deviation	Std. Error Mean
AgeAtDiagnosis	Spinal	85	60.1059	12.19682	1.32293
	Bulbar	23	60.3478	11.02727	2.29935

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
									Lower	Upper
AgeAtDiagnosis	Equal variances assumed	.070	.791	-.086	106	.932	-.24194	2.81188	-5.81677	5.33288
	Equal variances not assumed			-.091	37.889	.928	-.24194	2.65276	-5.61269	5.12881

Ranks

	Site of onset	N	Mean Rank	Sum of Ranks
Time from diagnosis to study entry (months)	Spinal	85	55.66	4731.50
	Bulbar	23	50.20	1154.50
	Total	108		

Test Statistics^a

	Time from diagnosis to study entry (months)
Mann-Whitney U	878.500
Wilcoxon W	1154.500
Z	-.744
Asymp. Sig. (2-tailed)	.457

a. Grouping Variable: Site of onset

Ratio Statistics for Time from diagnosis to study entry (months) / Site of onset

Median	95% Confidence Interval for Median			Price Related Differential	Coefficient of Dispersion	Coefficient of Variation
	Lower Bound	Upper Bound	Actual Coverage			Median Centered
7.000	6.000	10.500	95.7%	1.124	1.629	289.5%

The confidence interval for the median is constructed without any distribution assumptions. The actual coverage level may be greater than the specified level.

Baseline Measurements

Baseline	Distribution	Outliers	Missing
SNIP	Non parametric	0	2
PCF	Normal	0	4
SVC	Non parametric	0	4
SVC%	Non parametric	0	4
ALSFRS-R	Non parametric	n=4 (14,24,55,58)	0

Case Processing Summary

	Cases					
	Included		Excluded		Total	
	N	Percent	N	Percent	N	Percent
SNIP	106	98.1%	2	1.9%	108	100.0%
SVC%	104	96.3%	4	3.7%	108	100.0%
ALSFRS-R	108	100.0%	0	0.0%	108	100.0%

Report

	SNIP	SVC%	ALSFRS-R
N	106	104	108
Maximum	122	124.00%	47
Minimum	5	20.00%	8
Median	45.00	81.0000%	36.00

Case Processing Summary

	Cases					
	Included		Excluded		Total	
	N	Percent	N	Percent	N	Percent
PCF	104	96.3%	4	3.7%	108	100.0%

Report

PCF

N	Mean	Std. Deviation
104	346.44	153.274

Group Statistics

	Gender	N	Mean	Std. Deviation	Std. Error Mean
PCF	Female	37	262.70	117.631	19.338
	Male	67	392.69	151.703	18.534

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
									Lower	Upper
PCF	Equal variances assumed	2.144	.146	-4.513	102	.000	-129.984	28.803	-187.114	-72.853
	Equal variances not assumed			-4.853	90.745	.000	-129.984	26.785	-183.192	-76.776

Ranks

	Gender	N	Mean Rank	Sum of Ranks
SNIP	Female	37	46.04	1703.50
	Male	69	57.50	3967.50
	Total	106		

Test Statistics^a

	SNIP
Mann-Whitney U	1000.500
Wilcoxon W	1703.500
Z	-1.830
Asymp. Sig. (2-tailed)	.067

a. Grouping Variable: Gender

Ranks

	Gender	N	Mean Rank	Sum of Ranks
SVC%	Female	37	53.68	1986.00
	Male	67	51.85	3474.00
	Total	104		

Test Statistics^a

	SVC%
Mann-Whitney U	1196.000
Wilcoxon W	3474.000
Z	-.295
Asymp. Sig. (2-tailed)	.768

a. Grouping Variable: Gender

Ranks

	Gender	N	Mean Rank	Sum of Ranks
ALSFRS-R	Female	37	52.28	1934.50
	Male	71	55.65	3951.50
	Total	108		

Test Statistics^a

	ALSFRS-R
Mann-Whitney U	1231.500
Wilcoxon W	1934.500
Z	-.532
Asymp. Sig. (2-tailed)	.595

a. Grouping Variable: Gender

Ratio Statistics for SNIP / Gender

Median	95% Confidence Interval for Median			Price Related Differential	Coefficient of Dispersion	Coefficient of Variation
	Lower Bound	Upper Bound	Actual Coverage			Median Centered
31.000	26.500	37.000	95.9%	1.063	.526	66.0%

The confidence interval for the median is constructed without any distribution assumptions. The actual coverage level may be greater than the specified level.

Ratio Statistics for SVC% / Gender

Median	95% Confidence Interval for Median			Price Related Differential	Coefficient of Dispersion	Coefficient of Variation
	Lower Bound	Upper Bound	Actual Coverage			Median Centered
46.500	42.000	49.500	96.1%	1.118	.424	58.4%

The confidence interval for the median is constructed without any distribution assumptions. The actual coverage level may be greater than the specified level.

Ratio Statistics for ALSFRS-R / Gender

Median	95% Confidence Interval for Median			Price Related Differential	Coefficient of Dispersion	Coefficient of Variation
	Lower Bound	Upper Bound	Actual Coverage			Median Centered
19.750	18.500	21.000	95.7%	1.108	.357	50.4%

The confidence interval for the median is constructed without any distribution assumptions. The actual coverage level may be greater than the specified level.

Group Statistics

	SiteOfOnset	N	Mean	Std. Deviation	Std. Error Mean
PCF	Spinal	81	366.79	149.556	16.617
	Bulbar	23	274.78	147.521	30.760

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
									Lower	Upper
PCF	Equal variances assumed	.174	.677	2.611	102	.010	92.008	35.233	22.124	161.891
	Equal variances not assumed			2.632	35.874	.012	92.008	34.962	21.093	162.922

Ranks

	SiteOfOnset	N	Mean Rank	Sum of Ranks
SNIP	Spinal	83	53.62	4450.50
	Bulbar	23	53.07	1220.50
	Total	106		

Test Statistics^a

	SNIP
Mann-Whitney U	944.500
Wilcoxon W	1220.500
Z	-.077
Asymp. Sig. (2-tailed)	.939

a. Grouping Variable:
SiteOfOnset

Ranks

	SiteOfOnset	N	Mean Rank	Sum of Ranks
SVC%	Spinal	81	53.85	4362.00
	Bulbar	23	47.74	1098.00
	Total	104		

Test Statistics^a

	SVC%
Mann-Whitney U	822.000
Wilcoxon W	1098.000
Z	-.858
Asymp. Sig. (2-tailed)	.391

a. Grouping Variable:
SiteOfOnset

Ranks

	SiteOfOnset	N	Mean Rank	Sum of Ranks
ALSFRS-R	Spinal	85	54.16	4604.00
	Bulbar	23	55.74	1282.00
	Total	108		

Test Statistics^a

	ALSFRS-R
Mann-Whitney U	949.000
Wilcoxon W	4604.000
Z	-.214
Asymp. Sig. (2-tailed)	.830

a. Grouping Variable:
SiteOfOnset

Ratio Statistics for SNIP / SiteOfOnset

Median	95% Confidence Interval for Median			Price Related Differential	Coefficient of Dispersion	Coefficient of Variation
	Lower Bound	Upper Bound	Actual Coverage			Median Centered
35.500	32.000	46.000	95.9%	1.087	.680	91.9%

The confidence interval for the median is constructed without any distribution assumptions. The actual coverage level may be greater than the specified level.

Ratio Statistics for SVC% / SiteOfOnset

Median	95% Confidence Interval for Median			Price Related Differential	Coefficient of Dispersion	Coefficient of Variation
	Lower Bound	Upper Bound	Actual Coverage			Median Centered
72.000	56.000	81.000	96.1%	1.094	.347	40.3%

The confidence interval for the median is constructed without any distribution assumptions. The actual coverage level may be greater than the specified level.

Ratio Statistics for ALSFRS-R / SiteOfOnset

Median	95% Confidence Interval for Median			Price Related Differential	Coefficient of Dispersion	Coefficient of Variation
	Lower Bound	Upper Bound	Actual Coverage			Median Centered
34.000	30.000	36.000	95.7%	1.085	.236	30.7%

The confidence interval for the median is constructed without any distribution assumptions. The actual coverage level may be greater than the specified level.

Respiratory Muscle Strength and Function, Cough Strength and Physical Function

Linear mixed model fit by maximum likelihood t-tests use Satterthwaite approximations to degrees of freedom [lmerMod]

Formula: SNIP ~ device1 + time + Site + age1 + DiagStudy + Sex1 + (1 + time | id)

Data: RespData

AIC BIC logLik deviance df.resid

2774.8 2820.7 -1375.4 2750.8 326

Scaled residuals:

Min	1Q	Median	3Q	Max
-2.88246	-0.35369	-0.02545	0.37737	2.52996

Random effects:

Groups	Name	Variance	Std.Dev.	Corr
id	(Intercept)	656.655	25.625	
	time	3.302	1.817	-0.09
Residual		50.715	7.121	

Number of obs: 338, groups: id, 107

Fixed effects:

	Estimate	Std. Error	df	t value	Pr(> t)
(Intercept)	87.6787	9.7358	106.7300	9.006	9.33e-15 ***
device1M-IE	-24.6234	6.9764	106.2200	-3.530	0.000617 ***
device1LVR	-15.2100	6.0054	106.8000	-2.533	0.012772 *
time	-1.5600	0.2658	74.6800	-5.869	1.13e-07 ***
SiteBulbar	-3.3356	6.3298	106.5500	-0.527	0.599312
age1	-0.8922	0.2386	105.9900	-3.739	0.000300 ***
DiagStudy	-0.2395	0.1368	106.8900	-1.751	0.082791 .
Sex1M	10.4754	5.5457	106.6200	1.889	0.061621 .

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:

	(Intr)	d1M-IE	dv1LVR	time	StBlbr	age1	DgStdy
device1M-IE	0.010						
device1LVR	-0.086	0.292					
time	-0.046	0.000	0.003				
SiteBulbar	-0.291	-0.033	-0.061	0.005			
age1	-0.814	-0.191	-0.109	0.001	0.074		
DiagStudy	-0.121	0.008	0.038	-0.004	0.132	-0.144	
Sex1M	-0.556	-0.082	-0.070	0.004	0.208	0.231	-0.027

>

Linear mixed model fit by maximum likelihood t-tests use Satterthwaite

approximations to degrees of freedom [lmerMod]

Formula: PCF ~ device1 + time + Site + age1 + DiagStudy + Sex1 + (1 + time | id)

Data: RespData

AIC	BIC	logLik	deviance	df.resid
3880.8	3926.9	-1928.4	3856.8	331

Scaled residuals:

Min	1Q	Median	3Q	Max
-2.47986	-0.40991	0.00085	0.41130	2.53306

Random effects:

Groups	Name	Variance	Std.Dev.	Corr
id	(Intercept)	11446.9	106.99	
	time	141.5	11.89	0.06
Residual		1068.3	32.69	

Number of obs: 343, groups: id, 108

Fixed effects:

	Estimate	Std. Error	df	t value	Pr(> t)
(Intercept)	534.4099	40.3246	103.6400	13.253	< 2e-16 ***
device1M-IE	-124.7500	29.6925	104.4300	-4.201	5.60e-05 ***
device1LVR	-46.1958	25.6214	106.0600	-1.803	0.074225 .
time	-10.4030	1.5439	66.7800	-6.738	4.50e-09 ***
SiteBulbar	-81.9523	26.8536	103.9000	-3.052	0.002888 **
age1	-5.5570	0.9901	104.2100	-5.613	1.66e-07 ***
DiagStudy	-1.0053	0.5852	106.9400	-1.718	0.088731 .
Sex1M	88.8296	23.6008	104.6700	3.764	0.000276 ***

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:

	(Intr)	d1M-IE	dv1LVR	time	StBlbr	age1	DgStdy
device1M-IE		0.015					
device1LVR		-0.075	0.292				
time		-0.006	0.007	0.005			
SiteBulbar		-0.286	-0.033	-0.065	0.003		

```

age1      -0.805 -0.202 -0.128 -0.008  0.063
DiagStudy -0.119  0.009  0.045 -0.005  0.130 -0.156
Sex1M     -0.573 -0.084 -0.072 -0.011  0.205  0.240 -0.026

```

>

Linear mixed model fit by maximum likelihood t-tests use

Satterthwaite approximations to degrees of freedom [lmerMod]

Formula: svc ~ device1 + time + Site + age1 + DiagStudy + Sex1 + (1 + time | id)

Data: RespData

```

      AIC      BIC  logLik deviance df.resid
2778.3  2824.2 -1377.1  2754.3     326

```

Scaled residuals:

```

      Min      1Q  Median      3Q      Max
-2.9828 -0.3557 -0.0037  0.4268  3.1623

```

Random effects:

```

Groups  Name      Variance Std.Dev. Corr
id      (Intercept) 463.626  21.532
        time        4.292   2.072  -0.18
Residual          58.497   7.648

```

Number of obs: 338, groups: id, 108

Fixed effects:

```

      Estimate Std. Error    df t value Pr(>|t|)
(Intercept)  97.5965    7.9866 104.7700 12.220 < 2e-16 ***
device1M-IE -25.3896    5.8573 103.6300 -4.335 3.39e-05 ***
device1LVR  -14.9942    5.0532 105.3500 -2.967 0.00372 **
time         -1.4575    0.2951  73.1300 -4.939 4.82e-06 ***
SiteBulbar   -7.0468    5.3134 104.4400 -1.326 0.18765
age1         -0.1119    0.1952 103.2400 -0.573 0.56776
DiagStudy    -0.3313    0.1153 105.6400 -2.875 0.00489 **
Sex1M        -2.9213    4.6608 104.3900 -0.627 0.53218

```

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:

```

(Intr) d1M-IE dv1LVR time StBlbr age1 DgStdY
device1M-IE 0.012
device1LVR -0.081 0.291
time -0.074 -0.001 -0.002
SiteBulbar -0.287 -0.034 -0.060 0.009
age1 -0.802 -0.198 -0.124 0.007 0.062
DiagStudy -0.119 0.007 0.044 -0.012 0.131 -0.156
Sex1M -0.572 -0.080 -0.064 0.004 0.211 0.237 -0.024

>

model1 = lmer(ALSFRS.R~device1 + time + Site + age1+ DiagStudy+ Sex1 +
(1 +time|id),+ data=RespData, REML=FALSE)
> summary(model1)
Linear mixed model fit by maximum likelihood t-tests use Satterthwaite
approximations to degrees of freedom [lmerMod]
Formula: ALSFRS.R ~ device1 + time + Site + age1 + DiagStudy + Sex1 +
(1 + time | id) Data: RespData

AIC BIC logLik deviance df.resid
1809.2 1855.2 -892.6 1785.2 330

Scaled residuals:
Min 1Q Median 3Q Max
-3.4003 -0.3458 -0.0043 0.3352 3.4704

Random effects:
Groups Name Variance Std.Dev. Corr
id (Intercept) 43.240 6.5757
time 0.489 0.6993 0.05
Residual 1.716 1.3099
Number of obs: 342, groups: id, 108

Fixed effects:
Estimate Std. Error df t value Pr(>|t|)
(Intercept) 38.54877 2.43595 107.18000 15.825 < 2e-16 ***
device1M-IE -7.55829 1.79347 107.74000 -4.214 5.22e-05 ***
device1LVR -4.26595 1.54040 107.74000 -2.769 0.006615 **
time -0.80162 0.08332 67.06000 -9.621 2.98e-14 ***

```

SiteBulbar -1.05486 1.62236 107.41000 -0.650 0.516952
 age1 -0.01633 0.05975 107.28000 -0.273 0.785178
 DiagStudy -0.13969 0.03514 108.11000 -3.976 0.000127 ***
 Sex1M 1.08700 1.42454 107.74000 0.763 0.447102

 Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:

(Intr) d1M-IE dv1LVR time StBlbr age1 DgStdy
 device1M-IE 0.017
 device1LVR -0.075 0.293
 time 0.002 0.005 0.006
 SiteBulbar -0.286 -0.035 -0.065 0.000
 age1 -0.806 -0.203 -0.124 -0.007 0.064
 DiagStudy -0.121 0.009 0.036 0.002 0.131 -0.152
 Sex1M -0.572 -0.085 -0.075 -0.006 0.206 0.241 -0.028

>

Chest Infection Frequency and Antibiotic Use

Case Processing Summary

	Cases					
	Valid		Missing		Total	
	N	Percent	N	Percent	N	Percent
GPReportChestInfection *	57	52.8%	51	47.2%	108	100.0%
SelfReportChestInfection						

GPReportChestInfection * SelfReportChestInfection

Crosstabulation

Count

		SelfReportChestInfection		Total
		Yes	No	
GPReportChestInfection	Yes	14	14	28
	No	6	23	29
Total		20	37	57

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)	Exact Sig. (2- sided)	Exact Sig. (1- sided)
Pearson Chi-Square	5.373 ^a	1	.020	.028	.020
Continuity Correction ^b	4.163	1	.041		
Likelihood Ratio	5.485	1	.019		
Fisher's Exact Test					
Linear-by-Linear Association	5.279	1	.022		
N of Valid Cases	57				

a. 0 cells (.0%) have expected count less than 5. The minimum expected count is 9.82.

b. Computed only for a 2x2 table

Symmetric Measures

		Value	Approximate Significance
Nominal by	Phi	.307	.020
Nominal	Cramer's V	.307	.020
N of Valid Cases		57	

Prescribed a Device

	Distribution	Outliers	Missing
Age	Normal	0	0
Age male	Normal	1 (22)	
Age female	Normal	0	
Time since diagnosis to receiving device	Non parametric	n=2 (23,95)	0
SNIP	Normal	0	5
PCF	Normal	0	0
SVC	Normal	n=2 (100, 106)	5
SVC%	Normal	0	5
ALSFRS-R	Normal	1 (17)	5

Not Prescribed a Device

	Distribution	Outliers	Missing
Age	Normal	0	0
Age male	Normal	0	0
Age female	Normal	2 (17, 25)	0
Time since diagnosis to receiving device	Non parametric	n=7 (20,89,25,85,59,18,53)	0
SNIP	Non parametric	0	5
PCF	Normal	0	0
SVC			
SVC%	Normal	0	0
ALSFRS-R	Non parametric	5 (46,50,98,54,14)	5

Statistics

Timesincediagnosis to device

Months

N	Valid	32
	Missing	0
Median		11.0000
Minimum		1.00
Maximum		60.00

Case Processing Summary

		Cases					
		Included		Excluded		Total	
		N	Percent	N	Percent	N	Percent
Device	Age	30	100.0%	0	0.0%	30	100.0%
No Device	Age	60	100.0%	0	0.0%	60	100.0%

Report

Age

DeviceOrNoDevice	Mean	N	Std. Deviation
Device	63.0000	30	10.19466
No Device	60.2000	60	12.84431

Report

TimeSinceDiagnosisToStudyEntry

DeviceOrNoDevice	N	Maximum	Minimum	Median
Device	30	55.00	.00	6.5000
No Device	60	90.00	.00	7.5000

Ranks

	Gender	N	Mean Rank	Sum of Ranks
Timesincediagnosis to deviceMonths	Female	11	17.09	188.00
	Male	21	16.19	340.00
	Total	32		

Test Statistics^a

	Timesincediagnosis to deviceMonths
Mann-Whitney U	109.000
Wilcoxon W	340.000
Z	-.258
Asymp. Sig. (2-tailed)	.796
Exact Sig. [2*(1-tailed Sig.)]	.815 ^b

a. Grouping Variable: Gender

b. Not corrected for ties.

Ratio Statistics for TimesincediagnostodeviceMonths / Gender

Median	95% Confidence Interval for Median			Price Related Differential	Coefficient of Dispersion	Coefficient of Variation
	Lower Bound	Upper Bound	Actual Coverage			Median Centered
5.750	4.000	12.000	98.0%	1.091	1.212	180.9%

The confidence interval for the median is constructed without any distribution assumptions. The actual coverage level may be greater than the specified level.

Report

TimesincediagnostodeviceMonths

Gender	N	Maximum	Minimum	Median
Female	11	32.00	1.00	12.0000
Male	21	60.00	2.00	10.0000
Total	32	60.00	1.00	11.0000

Group Statistics

DeviceOrNoDevice Gender			N	Mean	Std. Deviation	Std. Error Mean
Device	Age	Female	10	60.5000	11.84389	3.74537
		Male	20	64.2500	9.34077	2.08866
No Device	Age	Female	22	67.5455	8.60082	1.83370
		Male	38	55.9474	13.05487	2.11778

Independent Samples Test

DeviceOrNoDevice			Levene's Test for Equality of Variances		t-test for Equality of Means						
			F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
										Lower	Upper
Device	Age	Equal variances assumed	.768	.388	-.948	28	.351	-3.75000	3.95527	-11.85201	4.35201
		Equal variances not assumed			-.874	14.791	.396	-3.75000	4.28839	-12.90176	5.40176
No Device	Age	Equal variances assumed	4.861	.031	3.719	58	.000	11.59809	3.11854	5.35564	17.84053
		Equal variances not assumed			4.140	56.913	.000	11.59809	2.80133	5.98834	17.20784

Ranks

DeviceOrNoDevice		Gender	N	Mean Rank	Sum of Ranks
Device	TimeSinceDiagnosisToStudyEntry	Female	10	16.60	166.00
		Male	20	14.95	299.00
		Total	30		
No Device	TimeSinceDiagnosisToStudyEntry	Female	22	30.82	678.00
		Male	38	30.32	1152.00
		Total	60		

Test Statistics^a

DeviceOrNoDevice		TimeSinceDiagnosisToStudyEntry
Device	Mann-Whitney U	89.000
	Wilcoxon W	299.000
	Z	-.485
	Asymp. Sig. (2-tailed)	.628
	Exact Sig. [2*(1-tailed Sig.)]	.650 ^b
No Device	Mann-Whitney U	411.000
	Wilcoxon W	1152.000
	Z	-.108
	Asymp. Sig. (2-tailed)	.914

a. Grouping Variable: Gender

b. Not corrected for ties.

Independent Samples Test

DeviceOrNoDevice			Levene's Test for Equality of Variances		t-test for Equality of Means						
			F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
										Lower	Upper
Device	Age	Equal variances assumed	.014	.906	-.379	28	.708	-1.92000	5.06978	-12.30497	8.46497
		Equal variances not assumed			-.393	5.938	.708	-1.92000	4.87945	-13.88975	10.04975
No Device	Age	Equal variances assumed	.015	.904	.496	58	.622	2.13729	4.31307	-6.49626	10.77084
		Equal variances not assumed			.504	15.103	.622	2.13729	4.24380	-6.90276	11.17734

Case Processing Summary

DeviceOrNoDevice		Cases					
		Included		Excluded		Total	
		N	Percent	N	Percent	N	Percent
Device	Age	30	100.0%	0	0.0%	30	100.0%
No Device	Age	60	100.0%	0	0.0%	60	100.0%

Report

Age

DeviceOrNoDevice	Mean	Std. Deviation
Device	63.0000	10.19466
No Device	60.2000	12.84431

Group Statistics

	Gender	N	Mean	Std. Deviation	Std. Error Mean
Age	Female	10	60.5000	11.84389	3.74537
	Male	20	64.2500	9.34077	2.08866

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
									Lower	Upper
Age	Equal variances assumed	.768	.388	-.948	28	.351	-3.75000	3.95527	-11.85201	4.35201
	Equal variances not assumed			-.874	14.791	.396	-3.75000	4.28839	-12.90176	5.40176

Group Statistics

DeviceOrNoDevice Siteofonset			N	Mean	Std. Deviation	Std. Error Mean
Device	Age	Spinal	25	62.6800	10.42721	2.08544
		Bulbar	5	64.6000	9.86408	4.41135
No Device	Age	Spinal	49	60.5918	12.98223	1.85460
		Bulbar	11	58.4545	12.65989	3.81710

Independent Samples Test

			Levene's Test for Equality of Variances		t-test for Equality of Means					
			F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference
										Lower Upper
Device	Age	Equal variances assumed	.014	.906	-.379	28	.708	-1.92000	5.06978	-12.30497 8.46497
		Equal variances not assumed			-.393	5.938	.708	-1.92000	4.87945	-13.88975 10.04975
No Device	Age	Equal variances assumed	.015	.904	.496	58	.622	2.13729	4.31307	-6.49626 10.77084
		Equal variances not assumed			.504	15.103	.622	2.13729	4.24380	-6.90276 11.17734

Ranks

	Site of onset	N	Mean Rank	Sum of Ranks
Timesince diagnosis to device Months	Spinal	26	16.37	425.50
	Bulbar	6	17.08	102.50
	Total	32		

Test Statistics^a

	Timesince diagnosis to device Months
Mann-Whitney U	74.500
Wilcoxon W	425.500
Z	-.169
Asymp. Sig. (2-tailed)	.866
Exact Sig. [2*(1-tailed Sig.)]	.869 ^b

a. Grouping Variable: Site of onset

b. Not corrected for ties.

Ratio Statistics for Timesince diagnosis to device Months / Site of onset

Median	95% Confidence Interval for Median			Price Related Differential	Coefficient of Dispersion	Coefficient of Variation
	Lower Bound	Upper Bound	Actual Coverage			Median Centered
9.500	6.000	14.000	98.0%	1.078	.936	158.6%

The confidence interval for the median is constructed without any distribution assumptions. The actual coverage level may be greater than the specified level.

Report

TimesincediagnosisistodeviceMonths

Site of onset	N	Maximum	Minimum	Median
Spinal	26	60.00	1.00	10.5000
Bulbar	6	32.00	2.00	14.0000
Total	32	60.00	1.00	11.0000

Case Processing Summary

	Cases					
	Included		Excluded		Total	
	N	Percent	N	Percent	N	Percent
SNIP	27	84.4%	5	15.6%	32	100.0%
PCF	32	100.0%	0	0.0%	32	100.0%
SVC%	27	84.4%	5	15.6%	32	100.0%
ALSFRS R	27	84.4%	5	15.6%	32	100.0%

Report

	SNIP	PCF	SVC%	ALSFRS R
Mean	31.96	241.41	60.59	29.6296
N	27	32	27	27
Std. Deviation	15.926	133.231	21.821	7.20122

Group Statistics

	Device	N	Mean	Std. Deviation	Std. Error Mean
SNIP	M-IE	12	25.25	16.939	4.890
	LVR	15	37.33	13.270	3.426

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
									Lower	Upper
SNIP	Equal variances assumed	.216	.646	-2.081	25	.048	-12.083	5.808	-24.045	-.122
	Equal variances not assumed			-2.024	20.559	.056	-12.083	5.971	-24.517	.350

Group Statistics

	Device	N	Mean	Std. Deviation	Std. Error Mean
PCF	M-IE	14	159.64	123.607	33.035
	LVR	18	305.00	104.389	24.605

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
									Lower	Upper
PCF	Equal variances assumed	1.602	.215	-3.606	30	.001	-145.357	40.310	-227.680	-63.034
	Equal variances not assumed			-3.529	25.437	.002	-145.357	41.191	-230.118	-60.596

Group Statistics

	Device	N	Mean	Std. Deviation	Std. Error Mean
SVC%	M-IE	12	54.58	22.797	6.581
	LVR	15	65.40	20.500	5.293

Independent Samples Test

	Levene's Test for Equality of Variances		t-test for Equality of Means						
	F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
								Lower	Upper
SVC%	.231	.635	-1.297	25	.207	-10.817	8.343	-27.999	6.366
			-1.281	22.453	.213	-10.817	8.446	-28.311	6.678

Group Statistics

	Device	N	Mean	Std. Deviation	Std. Error Mean
ALSFRS R	M-IE	12	28.1667	9.43719	2.72428
	LVR	15	30.8000	4.79881	1.23905

Independent Samples Test

	Levene's Test for Equality of Variances		t-test for Equality of Means						
	F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
								Lower	Upper
ALSFRSR	Equal variances assumed	3.505	-.942	25	.355	-2.63333	2.79507	-8.38988	3.12322
	Equal variances not assumed		-.880	15.500	.392	-2.63333	2.99282	-8.99448	3.72782

Ranks

	Device	N	Mean Rank	Sum of Ranks
Timesince diagnosis to device	M-IE	14	15.29	214.00
	LVR	18	17.44	314.00
	Total	32		

Test Statistics^a

	Timesince diagnosis to device Months
Mann-Whitney U	109.000
Wilcoxon W	214.000
Z	-.647
Asymp. Sig. (2-tailed)	.518
Exact Sig. [2*(1-tailed Sig.)]	.536 ^b

a. Grouping Variable: Device

b. Not corrected for ties.

Case Processing Summary

	Cases					
	Included		Excluded		Total	
	N	Percent	N	Percent	N	Percent
Timesince diagnosis to device Months * Device	32	100.0%	0	0.0%	32	100.0%

Report

Timesince diagnosis to device Months

Device	N	Minimum	Maximum	Median
M-IE	14	2.00	37.00	10.5000
LVR	18	1.00	60.00	11.5000
Total	32	1.00	60.00	11.0000

Case Processing Summary

	Cases					
	Valid		Missing		Total	
	N	Percent	N	Percent	N	Percent
Device * Site of onset	32	100.0%	0	0.0%	32	100.0%

Device * Site of onset Crosstabulation

Count

	Site of onset		Total
	Spinal	Bulbar	
Device M-IE	9	5	14
LVR	17	1	18
Total	26	6	32

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	4.702 ^a	1	.030	.064	.043
Continuity Correction ^b	2.930	1	.087		
Likelihood Ratio	4.912	1	.027		
Fisher's Exact Test					
Linear-by-Linear Association	4.555	1	.033		
N of Valid Cases	32				

a. 2 cells (50.0%) have expected count less than 5. The minimum expected count is 2.63.

b. Computed only for a 2x2 table

Symmetric Measures

	Value	Approximate Significance
Nominal by Phi	-.383	.030
Nominal Cramer's V	.383	.030
N of Valid Cases	32	

Group Statistics

	Site of onset	N	Mean	Std. Deviation	Std. Error Mean
SNIP	Spinal	22	32.45	14.368	3.063
	Bulbar	5	29.80	23.616	10.561

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
									Lower	Upper
SNIP	Equal variances assumed	.953	.338	.331	25	.744	2.655	8.029	-13.882	19.191
	Equal variances not assumed			.241	4.695	.819	2.655	10.997	-26.174	31.483

Group Statistics

	Site of onset	N	Mean	Std. Deviation	Std. Error Mean
PCF	Spinal	26	271.73	113.762	22.311
	Bulbar	6	110.00	140.855	57.504

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
									Lower	Upper
PCF	Equal variances assumed	.008	.930	3.008	30	.005	161.731	53.764	51.930	271.532
	Equal variances not assumed			2.622	6.589	.036	161.731	61.680	14.015	309.447

Group Statistics

	Site of onset	N	Mean	Std. Deviation	Std. Error Mean
SVC%	Spinal	22	63.86	17.799	3.795
	Bulbar	5	46.20	33.380	14.928

Independent Samples Test

	Levene's Test for Equality of Variances		t-test for Equality of Means						
	F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
								Lower	Upper
SVC% Equal variances assumed	5.992	.022	1.691	25	.103	17.664	10.444	-3.846	39.173
			1.147	4.530	.308	17.664	15.403	-23.198	58.525

Group Statistics

	Siteofonse t	N	Mean	Std. Deviation	Std. Error Mean
ALSFRS R	Spinal	22	30.3636	5.80267	1.23713
	Bulbar	5	26.4000	12.01249	5.37215

Independent Samples Test

	Levene's Test for Equality of Variances		t-test for Equality of Means						
	F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
								Lower	Upper
ALSFRSR									
Equal variances assumed	3.353	.079	1.116	25	.275	3.96364	3.55097	-3.34973	11.27700
Equal variances not assumed			.719	4.433	.508	3.96364	5.51276	-10.77013	18.69740

Ranks

	Site of onset	N	Mean Rank	Sum of Ranks
Times since diagnosis to device Months	Spinal	26	16.37	425.50
	Bulbar	6	17.08	102.50
	Total	32		

Test Statistics^a

	Timesince diagnosis to device Months
Mann-Whitney U	74.500
Wilcoxon W	425.500
Z	-.169
Asymp. Sig. (2-tailed)	.866
Exact Sig. [2*(1-tailed Sig.)]	.869 ^b

a. Grouping Variable: Site of onset

b. Not corrected for ties.

Case Processing Summary

	Cases					
	Included		Excluded		Total	
	N	Percent	N	Percent	N	Percent
Timesince diagnosis to device Months * Site of onset	32	100.0%	0	0.0%	32	100.0%

Report

Timesince diagnosis to device Months

Site of onset	N	Minimum	Maximum	Median
Spinal	26	1.00	60.00	10.5000
Bulbar	6	2.00	32.00	14.0000
Total	32	1.00	60.00	11.0000

Ratio Statistics for Timesincediagnosis to deviceMonths / Site of onset

Median	95% Confidence Interval for Median			Price Related Differential	Coefficient of Dispersion	Coefficient of Variation
	Lower Bound	Upper Bound	Actual Coverage			Median Centered
9.500	6.000	14.000	98.0%	1.078	.936	158.6%

The confidence interval for the median is constructed without any distribution assumptions. The actual coverage level may be greater than the specified level.

Case Processing Summary

	Cases					
	Valid		Missing		Total	
	N	Percent	N	Percent	N	Percent
Site of onset * Device or No Device	90	100.0%	0	0.0%	90	100.0%

Site of onset * Device or No Device Crosstabulation

			DeviceOrNoDevice		Total
			Device	No Device	
Siteofonset	Spinal	Count	25	49	74
		% within Siteofonset	33.8%	66.2%	100.0%
		% within DeviceOrNoDevice	83.3%	81.7%	82.2%
		% of Total	27.8%	54.4%	82.2%
	Bulbar	Count	5	11	16
		% within Siteofonset	31.3%	68.8%	100.0%
		% within DeviceOrNoDevice	16.7%	18.3%	17.8%
		% of Total	5.6%	12.2%	17.8%
Total	Count	30	60	90	
	% within Siteofonset	33.3%	66.7%	100.0%	
	% within DeviceOrNoDevice	100.0%	100.0%	100.0%	
	% of Total	33.3%	66.7%	100.0%	

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	.038 ^a	1	.845	1.000	.547
Continuity Correction ^b	.000	1	1.000		
Likelihood Ratio	.038	1	.845		
Fisher's Exact Test					
Linear-by-Linear Association	.038	1	.846		
N of Valid Cases	90				

a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 5.33.

b. Computed only for a 2x2 table

Symmetric Measures

	Value	Approximate Significance
Nominal by Phi	.021	.845
Nominal Cramer's V	.021	.845
N of Valid Cases	90	

Group Statistics

	DeviceOrNoDevi ce	N	Mean	Std. Deviation	Std. Error Mean
Age	Device	30	63.0000	10.19466	1.86128
	No Device	60	60.2000	12.84431	1.65819

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
									Lower	Upper
Age	Equal variances assumed	2.243	.138	1.040	88	.301	2.80000	2.69127	-2.54834	8.14834
	Equal variances not assumed			1.123	71.243	.265	2.80000	2.49278	-2.17018	7.77018

Group Statistics

Gender			DeviceOrNoDevice	N	Mean	Std. Deviation	Std. Error Mean
Female	Age	Device	Device	10	60.5000	11.84389	3.74537
			No Device	22	67.5455	8.60082	1.83370
Male	Age	Device	Device	20	64.2500	9.34077	2.08866
			No Device	38	55.9474	13.05487	2.11778

Independent Samples Test

			Levene's Test for Equality of Variances		t-test for Equality of Means					
			F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference
										Lower Upper
Female	Age	Equal variances assumed	1.741	.197	-1.907	30	.066	-7.04545	3.69501	-14.59168 .50077
		Equal variances not assumed			-1.689	13.499	.114	-7.04545	4.17016	-16.02078 1.92987
Male	Age	Equal variances assumed	2.621	.111	2.520	56	.015	8.30263	3.29435	1.70326 14.90200
		Equal variances not assumed			2.791	50.655	.007	8.30263	2.97447	2.33014 14.27512

Ranks

	DeviceOrNoDevice	N	Mean Rank	Sum of Ranks
TimeSinceDiagnosisToStudyEntry	Device	30	44.50	1335.00
	No Device	60	46.00	2760.00
	Total	90		

Test Statistics^a

	TimeSinceDiagnosisToStudyEntry
Mann-Whitney U	870.000
Wilcoxon W	1335.000
Z	-.257
Asymp. Sig. (2-tailed)	.797

a. Grouping Variable:

DeviceOrNoDevice

Case Processing Summary

	Cases					
	Included		Excluded		Total	
	N	Percent	N	Percent	N	Percent
TimeSinceDiagnosisToStudyEntry * DeviceOrNoDevice	90	100.0%	0	0.0%	90	100.0%

Report

TimeSinceDiagnosisToStudyEntry

DeviceOrNoDevice	N	Minimum	Maximum	Median
Device	30	.00	55.00	6.5000
No Device	60	.00	90.00	7.5000
Total	90	.00	90.00	7.0000

Ratio Statistics for TimeSinceDiagnosisToStudyEntry / DeviceOrNoDevice

Median	95% Confidence Interval for Median			Price Related Differential	Coefficient of Dispersion	Coefficient of Variation
	Lower Bound	Upper Bound	Actual Coverage			Median Centered
5.000	3.500	7.000	95.5%	1.068	1.494	253.6%

The confidence interval for the median is constructed without any distribution assumptions. The actual coverage level may be greater than the specified level.

Ranks

Siteofonset	DeviceOrNoDevice	N	Mean Rank	Sum of Ranks
Spinal TimeSinceDiagnosisToStudyEntry	Device	25	35.62	890.50
	No Device	49	38.46	1884.50
	Total	74		
Bulbar TimeSinceDiagnosisToStudyEntry	Device	5	9.40	47.00
	No Device	11	8.09	89.00
	Total	16		

Test Statistics^a

Siteofonset		TimeSinceDiagnosisToStudyEntry
Spinal	Mann-Whitney U	565.500
	Wilcoxon W	890.500
	Z	-.538
	Asymp. Sig. (2-tailed)	.591
Bulbar	Mann-Whitney U	23.000
	Wilcoxon W	89.000
	Z	-.512
	Asymp. Sig. (2-tailed)	.608
	Exact Sig. [2*(1-tailed Sig.)]	.661 ^b

a. Grouping Variable: DeviceOrNoDevice

b. Not corrected for ties.

Case Processing

Summary

Siteofonset		Count
Spinal	Overall	74
	Excluded	0
	Total	74
Bulbar	Overall	16
	Excluded	0
	Total	16

Ratio Statistics for TimeSinceDiagnosisToStudyEntry / DeviceOrNoDevice

Site of onset	Median	95% Confidence Interval for Median			Price Related Differential	Coefficient of Dispersion	Coefficient of Variation
		Lower Bound	Upper Bound	Actual Coverage			Median Centered
Spinal Bulbar	5.000	3.500	7.500	95.3%	1.057	1.588	270.8%
	5.000	1.000	12.000	97.9%	1.139	1.063	157.9%

The confidence interval for the median is constructed without any distribution assumptions. The actual coverage level may be greater than the specified level.

```
model2 = lmer(SNIP~LVR + time + Site + age1+ DiagStudy+ Sex1 + (1 +time|id),
+ data=RespData, REML=FALSE)
> summary(model2)
```

Linear mixed model fit by maximum likelihood t-tests use Satterthwaite approximations to

degrees of freedom [lmerMod]

Formula: SNIP ~ LVR + time + Site + age1 + DiagStudy + Sex1 + (1 + time | id)

Data: RespData

```
AIC      BIC    logLik deviance df.resid
2280.5  2320.4 -1129.3  2258.5     266
```

Scaled residuals:

```
      Min       1Q   Median       3Q      Max
-2.89565 -0.36910 -0.00801  0.39201  2.53075
```

Random effects:

```
Groups   Name      Variance Std.Dev. Corr
id       (Intercept) 716.894  26.775
        time         3.189   1.786  -0.10
Residual          50.256   7.089
```

Number of obs: 277, groups: id, 88

Fixed effects:

```
Estimate Std. Error    df t value Pr(>|t|)
```

```

(Intercept) 92.6819 11.1506 87.6200 8.312 1.10e-12 ***
LVRLVR -14.6276 6.2720 87.6600 -2.332 0.021981 *
time -1.5332 0.2914 62.2200 -5.262 1.87e-06 ***
SiteBulbar -9.0434 7.2383 87.6600 -1.249 0.214847
age1 -1.0184 0.2736 86.9000 -3.722 0.000351 ***
DiagStudy -0.1876 0.1557 87.9500 -1.205 0.231537
Sex1M 9.2011 6.4664 87.5600 1.423 0.158317
---
Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

```

Correlation of Fixed Effects:

```

      (Intr) LVRLVR time StBlbr age1 DgStdy
LVRLVR -0.052
time -0.046 0.002
SiteBulbar -0.291 -0.069 0.012
age1 -0.832 -0.124 -0.002 0.083
DiagStudy -0.059 0.051 -0.001 0.094 -0.192
Sex1M -0.602 -0.086 0.005 0.207 0.298 -0.082

```

```

` = lmer(PCF~LVR + time + Site + age1+ DiagStudy+ Sex1 + (1 +time|id),
+       data=RespData, REML=FALSE)

```

```
> summary(model2)
```

Linear mixed model fit by maximum likelihood t-tests use Satterthwaite approximations to

degrees of freedom [lmerMod]

Formula: PCF ~ LVR + time + Site + age1 + DiagStudy + Sex1 + (1 + time | id)

Data: RespData

```

      AIC      BIC logLik deviance df.resid
3173.5  3213.5 -1575.7  3151.5      270

```

Scaled residuals:

```

      Min      1Q   Median      3Q      Max

```

-2.54168 -0.39235 -0.00726 0.40856 2.33354

Random effects:

Groups	Name	Variance	Std.Dev.	Corr
id	(Intercept)	11857.1	108.89	
	time	142.0	11.92	-0.01
Residual		994.2	31.53	

Number of obs: 281, groups: id, 89

Fixed effects:

	Estimate	Std. Error	df	t value	Pr(> t)
(Intercept)	557.3239	44.7478	85.5900	12.455	< 2e-16 ***
LVRLVR	-45.3729	25.9583	87.1000	-1.748	0.08400 .
time	-10.7820	1.6969	58.4200	-6.354	3.44e-08 ***
SiteBulbar	-101.2615	29.7783	85.5300	-3.401	0.00102 **
age1	-5.9208	1.0987	85.9300	-5.389	6.11e-07 ***
DiagStudy	-0.6006	0.6465	87.9900	-0.929	0.35546
Sex1M	67.8517	26.7097	86.2000	2.540	0.01287 *

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:

	(Intr)	LVRLVR	time	StBlbr	age1	DgStdy
LVRLVR		-0.040				
time		-0.020	0.004			
SiteBulbar		-0.284	-0.073	0.004		
age1		-0.823	-0.144	-0.007	0.071	
DiagStudy		-0.056	0.058	-0.006	0.092	-0.203
Sex1M		-0.617	-0.089	-0.010	0.205	0.307

```
> model2 = lmer(SVC~LVR + time + Site + age1+ DiagStudy+ Sex1 + (1 +time|id),  
+ data=RespData, REML=FALSE)
```

```

> summary(model2)
Linear mixed model fit by maximum likelihood t-tests use Satterthwaite approximations to
degrees of freedom [lmerMod]
Formula: SVC ~ LVR + time + Site + age1 + DiagStudy + Sex1 + (1 + time | id)
Data: RespData

    AIC    BIC  logLik deviance df.resid
 439.7  479.6 -208.8  417.7    266

Scaled residuals:
    Min     1Q  Median     3Q     Max
-2.7191 -0.3746 -0.0422  0.4137  2.7271

Random effects:
Groups Name      Variance Std.Dev. Corr
id      (Intercept) 0.803703 0.89649
        time        0.004112 0.06413 0.06
Residual          0.068819 0.26233
Number of obs: 277, groups: id, 89

Fixed effects:
              Estimate Std. Error    df t value Pr(>|t|)
(Intercept)  4.058879   0.369177 84.660000 10.994 < 2e-16 ***
LVRLVR       -0.679667   0.213966 86.240000 -3.177 0.00207 **
time         -0.047617   0.010591 58.660000 -4.496 3.32e-05 ***
SiteBulbar   -0.418412   0.245679 84.750000 -1.703 0.09222 .
age1         -0.039416   0.009063 85.140000 -4.349 3.77e-05 ***
DiagStudy    -0.009016   0.005327 87.160000 -1.693 0.09412 .
Sex1M        0.974728   0.220328 85.420000  4.424 2.84e-05 ***
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:
      (Intr) LVRLVR time  StBlbr age1  DgStdy
LVRLVR  -0.040
time     -0.012 0.002
SiteBulbar -0.284 -0.073 0.002

```

```
age1      -0.823 -0.143 -0.007  0.071
DiagStudy -0.057  0.056 -0.009  0.092 -0.202
Sex1M     -0.618 -0.089 -0.010  0.205  0.307 -0.081
```

```
>
```

```
> model2 = lmer(ALSFRS.R~LVR + time + Site + age1+ DiagStudy+ Sex1 +
(1 +time|id),
+          data=RespData, REML=FALSE)
```

```
> summary(model2)
```

Linear mixed model fit by maximum likelihood t-tests use Satterthwaite approximations to

degrees of freedom [lmerMod]

Formula: ALSFRS.R ~ LVR + time + Site + age1 + DiagStudy + Sex1 + (1 + time | id)

Data: RespData

AIC	BIC	logLik	deviance	df.resid
1466.1	1506.1	-722.0	1444.1	270

Scaled residuals:

Min	1Q	Median	3Q	Max
-3.4720	-0.3482	0.0021	0.3489	3.6271

Random effects:

Groups	Name	Variance	Std.Dev.	Corr
id	(Intercept)	38.7914	6.2283	
	time	0.4595	0.6779	0.07
Residual		1.6072	1.2678	

Number of obs: 281, groups: id, 89

Fixed effects:

	Estimate	Std. Error	df	t value	Pr(> t)
(Intercept)	41.96254	2.53149	88.17000	16.576	< 2e-16 ***
LVRLVR	-3.81791	1.46419	88.80000	-2.608	0.01070 *
time	-0.76832	0.08941	53.09000	-8.593	1.26e-11 ***

SiteBulbar -2.84122 1.68657 88.60000 -1.685 0.09558 .
age1 -0.08814 0.06214 88.36000 -1.419 0.15956
DiagStudy -0.10886 0.03642 89.39000 -2.989 0.00361 **
Sex1M -1.08409 1.51133 88.79000 -0.717 0.47507

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:

(Intr) LVRLVR time StBlbr age1 DgStdy

LVRLVR -0.040

time 0.011 0.008

SiteBulbar -0.283 -0.073 -0.006

age1 -0.824 -0.141 -0.009 0.071

DiagStudy -0.058 0.050 0.003 0.094 -0.200

Sex1M -0.618 -0.092 -0.011 0.204 0.308 -0.084

Ranks

	DeviceOrNoDevice	N	Mean Rank	Sum of Ranks
Total No. Of Chest Infections	Device	48	58.34	2800.50
	No Device	60	51.43	3085.50
	Total	108		

Test Statistics^a

	Total No. Of Chest Infections
Mann-Whitney U	1255.500
Wilcoxon W	3085.500
Z	-1.386
Asymp. Sig. (2-tailed)	.166

a. Grouping Variable:

DeviceOrNoDevice

Ranks

	DeviceOrNoDevice	N	Mean Rank	Sum of Ranks
Total No. Of time anti biotics reported	Device	48	57.59	2764.50
	No Device	60	52.03	3121.50
	Total	108		

Test Statistics^a

	Total No. Of time anti biotics reported
Mann-Whitney U	1291.500
Wilcoxon W	3121.500
Z	-1.150
Asymp. Sig. (2-tailed)	.250

a. Grouping Variable:

DeviceOrNoDevice

Ratio Statistics for Total No. Of Chest Infections / DeviceOrNoDevice

	95% Confidence Interval for Median			Price Related Differential	Coefficient of Dispersion	Coefficient of Variation
	Lower Bound	Upper Bound	Actual Coverage			Median Centered
Median	.000	.000	95.7%	1.174	.	.

The confidence interval for the median is constructed without any distribution assumptions. The actual coverage level may be greater than the specified level.

Experience

	Distribution	Outliers	Missing
Age	Normal	0	0
Time since receiving device	Normal	0	0
Time since diagnosis (months)	Non parametric	0	0

Experience and Usability of Mechanical Insufflation Exsufflation and Lung Volume Recruitment in Amyotrophic Lateral Sclerosis SPSS Outputs

Case Processing Summary

	Cases					
	Valid		Missing		Total	
	N	Percent	N	Percent	N	Percent
Age	19	100.0%	0	0.0%	19	100.0%

Descriptives

		Statistic	Std. Error
Age	Mean	65.0526	2.24712
	95% Confidence Interval for Mean	Lower Bound	60.3316
		Upper Bound	
			69.7737
	5% Trimmed Mean	65.5585	
	Median	68.0000	
	Variance	95.942	
	Std. Deviation	9.79497	
	Minimum	41.00	
	Maximum	80.00	
	Range	39.00	
	Interquartile Range	13.00	
	Skewness	-.826	.524
	Kurtosis	.650	1.014

Group Statistics

	Gender	N	Mean	Std. Deviation	Std. Error Mean
Age	Female	10	64.6000	12.55388	3.96989
	Male	9	65.5556	6.16667	2.05556

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
									Lower	Upper
Age	Equal variances assumed	5.024	.039	-.207	17	.839	-.95556	4.62515	-10.71378	8.80266
	Equal variances not assumed			-.214	13.390	.834	-.95556	4.47049	-10.58495	8.67384

Case Processing Summary

	Cases					
	Valid		Missing		Total	
	N	Percent	N	Percent	N	Percent
Time since receiving device (days)	19	100.0%	0	0.0%	19	100.0%

Descriptives

			Statistic	Std. Error
Time since receiving device (days)	Mean		60.42	4.808
	95% Confidence Interval for Mean	Lower Bound	50.32	
		Upper Bound	70.52	
	5% Trimmed Mean		60.97	
	Median		62.00	
	Variance		439.257	
	Std. Deviation		20.958	
	Minimum		14	
	Maximum		97	
	Range		83	
	Interquartile Range		28	
	Skewness		-.350	.524
	Kurtosis		.076	1.014

Case Processing Summary

	Cases					
	Valid		Missing		Total	
	N	Percent	N	Percent	N	Percent
Timesincediagnosismonths	19	100.0%	0	0.0%	19	100.0%

Descriptives

			Statistic	Std. Error
Timesincediagnosismonths	Mean		13.6316	2.20739
	95% Confidence Interval for Mean	Lower Bound	8.9940	
		Upper Bound	18.2691	
	5% Trimmed Mean		12.8129	
	Median		11.0000	
	Variance		92.579	
	Std. Deviation		9.62180	
	Minimum		3.00	
	Maximum		39.00	
	Range		36.00	
	Interquartile Range		16.00	
	Skewness		1.155	.524
	Kurtosis		1.147	1.014

Alone or with family member

	Frequency	Percent	Valid Percent	Cumulative Percent
Valid Alone	7	36.8	36.8	36.8
Family Member/Carer	10	52.6	52.6	89.5
Alone and family/carers	2	10.5	10.5	100.0
Total	19	100.0	100.0	

Alone or with family member

Device	Frequency	Percent	Valid Percent	Cumulative Percent
M-IE Valid Alone	3	42.9	42.9	42.9
Family Member/Carer	3	42.9	42.9	85.7
Alone and family/carers	1	14.3	14.3	100.0
Total	7	100.0	100.0	
LVR Valid Alone	4	33.3	33.3	33.3
Family Member/Carer	7	58.3	58.3	91.7
Alone and family/carers	1	8.3	8.3	100.0
Total	12	100.0	100.0	

Alone or with family member

Site of onset			Frequency	Percent	Valid Percent	Cumulative Percent
Spinal	Valid	Alone	5	38.5	38.5	38.5
		Family Member/Carer	8	61.5	61.5	100.0
		Total	13	100.0	100.0	
Bulbar	Valid	Alone	2	33.3	33.3	33.3
		Family Member/Carer	2	33.3	33.3	66.7
		Alone and family/carers	2	33.3	33.3	100.0
		Total	6	100.0	100.0	

Ease of use

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Disagree	2	10.5	11.1	11.1
	Neutral	3	15.8	16.7	27.8
	Agree	13	68.4	72.2	100.0
	Total	18	94.7	100.0	
Missing	System	1	5.3		
Total		19	100.0		

Ease of use

Site of onset			Frequency	Percent	Valid Percent	Cumulative Percent
Spinal	Valid	Disagree	2	15.4	15.4	15.4
		Agree	11	84.6	84.6	100.0
		Total	13	100.0	100.0	
Bulbar	Valid	Neutral	3	50.0	60.0	60.0
		Agree	2	33.3	40.0	100.0
		Total	5	83.3	100.0	
	Missing	System	1	16.7		
	Total		6	100.0		

Ease of use

Device			Frequenc y	Percent	Valid Percent	Cumulative Percent
M-IE	Valid	Neutral	2	28.6	28.6	28.6
		Agree	5	71.4	71.4	100.0
		Total	7	100.0	100.0	
LVR	Valid	Disagree	2	16.7	18.2	18.2
		Neutral	1	8.3	9.1	27.3
		Agree	8	66.7	72.7	100.0
		Total	11	91.7	100.0	
	Missing	System	1	8.3		
Total			12	100.0		

Comfort

		Frequenc y	Percent	Valid Percent	Cumulative Percent
Valid	Disagree	3	15.8	16.7	16.7
	Neutral	3	15.8	16.7	33.3
	Agree	12	63.2	66.7	100.0
	Total	18	94.7	100.0	
Missing	System	1	5.3		
Total		19	100.0		

Comfort

Device			Frequency	Percent	Valid Percent	Cumulative Percent
M-IE	Valid	Disagree	2	28.6	28.6	28.6
		Neutral	2	28.6	28.6	57.1
		Agree	3	42.9	42.9	100.0
		Total	7	100.0	100.0	
LVR	Valid	Disagree	1	8.3	9.1	9.1
		Neutral	1	8.3	9.1	18.2
		Agree	9	75.0	81.8	100.0
		Total	11	91.7	100.0	
	Missing	System	1	8.3		
Total			12	100.0		

Comfort

Site of onset			Frequency	Percent	Valid Percent	Cumulative Percent
Spinal	Valid	Disagree	1	7.7	7.7	7.7
		Neutral	2	15.4	15.4	23.1
		Agree	10	76.9	76.9	100.0
		Total	13	100.0	100.0	
Bulbar	Valid	Disagree	2	33.3	40.0	40.0
		Neutral	1	16.7	20.0	60.0
		Agree	2	33.3	40.0	100.0
		Total	5	83.3	100.0	
	Missing	System	1	16.7		
Total			6	100.0		

Confidence

		Frequenc y	Percent	Valid Percent	Cumulative Percent
Valid	Disagree	2	10.5	11.1	11.1
	Neutral	4	21.1	22.2	33.3
	Agree	12	63.2	66.7	100.0
	Total	18	94.7	100.0	
Missing	System	1	5.3		
Total		19	100.0		

Confidence

Device			Frequenc y	Percent	Valid Percent	Cumulative Percent
M-IE	Valid	Neutral	3	42.9	42.9	42.9
		Agree	4	57.1	57.1	100.0
		Total	7	100.0	100.0	
LVR	Valid	Disagree	2	16.7	18.2	18.2
		Neutral	1	8.3	9.1	27.3
		Agree	8	66.7	72.7	100.0
		Total	11	91.7	100.0	
	Missing	System	1	8.3		
Total			12	100.0		

Confidence

Site of onset			Frequency	Percent	Valid Percent	Cumulative Percent
Spinal	Valid	Disagree	1	7.7	7.7	7.7
		Neutral	1	7.7	7.7	15.4
		Agree	11	84.6	84.6	100.0
		Total	13	100.0	100.0	
Bulbar	Valid	Disagree	1	16.7	20.0	20.0
		Neutral	3	50.0	60.0	80.0
		Agree	1	16.7	20.0	100.0
		Total	5	83.3	100.0	
	Missing	System	1	16.7		
Total			6	100.0		

Knowledge leaving clinic

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Disagree	1	5.3	5.6	5.6
	Agree	17	89.5	94.4	100.0
	Total	18	94.7	100.0	
Missing	System	1	5.3		
Total		19	100.0		

Knowledge leaving clinic

Device			Frequency	Percent	Valid Percent	Cumulative Percent
M-IE	Valid	Disagree	1	14.3	14.3	14.3
		Agree	6	85.7	85.7	100.0
		Total	7	100.0	100.0	
LVR	Valid	Agree	11	91.7	100.0	100.0
		Missing	System	1	8.3	
	Total		12	100.0		

Knowledge leaving clinic

Siteofonset			Frequency	Percent	Valid Percent	Cumulative Percent
Spinal	Valid	Disagree	1	7.7	7.7	7.7
		Agree	12	92.3	92.3	100.0
		Total	13	100.0	100.0	
Bulbar	Valid	Agree	5	83.3	100.0	100.0
	Missing	System	1	16.7		
	Total		6	100.0		

Cleaning

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Neutral	1	5.3	5.9	5.9
	Agree	16	84.2	94.1	100.0
	Total	17	89.5	100.0	
Missing	System	2	10.5		
Total		19	100.0		

Cleaning

Siteofonset			Frequency	Percent	Valid Percent	Cumulative Percent
Spinal	Valid	Agree	12	92.3	100.0	100.0
	Missing	System	1	7.7		
	Total		13	100.0		
Bulbar	Valid	Neutral	1	16.7	20.0	20.0
		Agree	4	66.7	80.0	100.0
		Total	5	83.3	100.0	
	Missing	System	1	16.7		
	Total		6	100.0		

Useofdevice

		Frequenc y	Percent	Valid Percent	Cumulative Percent
Valid	Device used	18	94.7	94.7	94.7
	Device not used	1	5.3	5.3	100.0
	Total	19	100.0	100.0	

Reported frequency

		Frequenc y	Percent	Valid Percent	Cumulative Percent
Valid	>3/day	1	5.3	5.3	5.3
	3/day	4	21.1	21.1	26.3
	2/day	5	26.3	26.3	52.6
	1/day	5	26.3	26.3	78.9
	1-6/week	1	5.3	5.3	84.2
	<4/month	2	10.5	10.5	94.7
	Not used	1	5.3	5.3	100.0
	Total	19	100.0	100.0	

Speech volume

		Frequenc y	Percent	Valid Percent	Cumulative Percent
Valid	Disagree	3	15.8	20.0	20.0
	Neutral	7	36.8	46.7	66.7
	Agree	5	26.3	33.3	100.0
	Total	15	78.9	100.0	
Missing	System	4	21.1		
Total		19	100.0		

Speech volume

Device			Frequency	Percent	Valid Percent	Cumulative Percent
M-IE	Valid	Disagree	2	28.6	33.3	33.3
		Neutral	1	14.3	16.7	50.0
		Agree	3	42.9	50.0	100.0
		Total	6	85.7	100.0	
	Missing	System	1	14.3		
	Total		7	100.0		
LVR	Valid	Disagree	1	8.3	11.1	11.1
		Neutral	6	50.0	66.7	77.8
		Agree	2	16.7	22.2	100.0
		Total	9	75.0	100.0	
	Missing	System	3	25.0		
	Total		12	100.0		

Speech volume

Site of onset			Frequency	Percent	Valid Percent	Cumulative Percent
Spinal	Valid	Disagree	1	7.7	8.3	8.3
		Neutral	7	53.8	58.3	66.7
		Agree	4	30.8	33.3	100.0
		Total	12	92.3	100.0	
	Missing	System	1	7.7		
	Total		13	100.0		
Bulbar	Valid	Disagree	2	33.3	66.7	66.7
		Agree	1	16.7	33.3	100.0
		Total	3	50.0	100.0	
	Missing	System	3	50.0		
	Total		6	100.0		

Cough stronger

		Frequenc y	Percent	Valid Percent	Cumulative Percent
Valid	Disagree	5	26.3	29.4	29.4
	Neutral	2	10.5	11.8	41.2
	Agree	10	52.6	58.8	100.0
	Total	17	89.5	100.0	
Missing	System	2	10.5		
Total		19	100.0		

Coughstrengthcategory

Device			Frequenc y	Percent	Valid Percent	Cumulative Percent
M-IE	Valid	Disagree	2	28.6	28.6	28.6
		Agree	5	71.4	71.4	100.0
		Total	7	100.0	100.0	
LVR	Valid	Disagree	3	25.0	37.5	37.5
		Agree	5	41.7	62.5	100.0
		Total	8	66.7	100.0	
	Missing	System	4	33.3		
	Total		12	100.0		

Cough stronger

Site of onset			Frequency	Percent	Valid Percent	Cumulative Percent
Spinal	Valid	Disagree	2	15.4	16.7	16.7
		Neutral	2	15.4	16.7	33.3
		Agree	8	61.5	66.7	100.0
		Total	12	92.3	100.0	
	Missing	System	1	7.7		
Total			13	100.0		
Bulbar	Valid	Disagree	3	50.0	60.0	60.0
		Agree	2	33.3	40.0	100.0
		Total	5	83.3	100.0	
	Missing	System	1	16.7		
	Total		6	100.0		

Adherence Device

Manual Records * Prototype Crosstabulation

			Prototype	Total
			Positive	
Manual Records	Negative	Count	7	7
		% within Manual Records	100.0%	100.0%
		% within Prototype	2.8%	2.8%
		% of Total	2.8%	2.8%
	Positive	Count	245	245
		% within Manual Records	100.0%	100.0%
		% within Prototype	97.2%	97.2%
		% of Total	97.2%	97.2%
Total	Count	252	252	
	% within Manual Records	100.0%	100.0%	
	% within Prototype	100.0%	100.0%	
	% of Total	100.0%	100.0%	