

USE OF THE INSPIRATORY MUSCLE TRAINER DEVICE (IMT) AFTER EXTUBATION IN A CRITICAL CARE SETTING

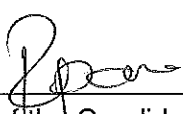
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A dissertation submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in fulfilment of the requirements for the degree of Masters of Science in Physiotherapy.

Johannesburg, 2015

DECLARATION

I, Nthabiseng Veronica Thupana, declare that this dissertation is my own work. It is being submitted for the degree of Masters of Science in Physiotherapy at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.



Signature of the Candidate

Date: 08 day of May 2015

ABSTRACT

Background: Mechanical ventilation (MV) and intensive care unit (ICU) admission are necessary medical interventions when required. However the effects of bed rest and immobility result in dysfunctions that occur within a very short period of time (Winkelman, 2007). The resultant diaphragmatic weakness results in weaning and extubation failure and may result in the need for re-intubation (Martin et al., 2013; Thille et al., 2013). In mechanically ventilated patients, inspiratory muscle training (IMT) has been administered to decrease weaning failure by increasing diaphragmatic strength (Cader et al., 2010). The use of IMT during prolonged MV reportedly improved the perception of dyspnoea, six minute walk test (6MWT) and the ability to perform activities of daily living (ADL) and the resultant quality of life (QOL) in some survivors of critical illness (Chang et al., 2005). The aim of this study was to establish the effect of the addition of IMT to standard in-hospital physiotherapy treatment on re-intubation rate and other outcomes of patients who were extubated after prolonged MV.

Method: A single-blinded randomised controlled trial was conducted using patients, who fitted the inclusion criteria for the trial, in the ICU of a quaternary hospital in Johannesburg. After extubation, the patients were randomly allocated to an intervention or control group using a computer generated randomisation list. Patients in the control group received standard in-patient physiotherapy rehabilitation. Those allocated to the intervention group received IMT therapy in addition to the standard in-patient physiotherapy management.

Results: The control group had a higher risk for mortality as measured by the APACHE II score; however their MV, ICU and hospital length of stay (LOS) was less than the intervention group. The effect of IMT on maximal inspiratory pressure (PiMax) was not statistically significant ($p=0.11$) between the intervention group and the control group over time at the different time points but might hold clinical significance as there was less deterioration in PiMax in the intervention group (2.4 cmH₂O) versus the control group (9.1 cmH₂O). Expiratory muscle strength had improved significantly (98.8 cmH₂O) for the intervention group at hospital discharge as compared to the control group (71.5 cmH₂O). This was statistically significant ($p=0.02$); however, this difference in maximal expiratory pressure (PeMax) between the groups was not noted at the one and three month assessments. The distance walked as assessed by the 6MWT had improved in the intervention group at the one month follow-up assessment (152 m) as compared to the control group (149.8 m). The intervention group were younger and had a longer LOS in ICU

and in hospital which might have resulted in decreased muscle strength; the predicted percentage of distance walked on the 6MWT could have been affected by these factors. Further to this, the decline in ability to perform the functional assessment as measured by the 6MWT could have resulted in the impairment or inability to perform ADL's. The intervention group scored higher than the control group when the health assessment questionnaire (HAQ) was assessed and the differences were statistically significant at each assessment. However this was not the case when the effect of IMT on quality of life (QOL) as measured by the HAQ was observed over time ($p=0.29$). At the discharge and three month time points respectively, the intervention group had a higher EQ-5D VAS rating (78.1%; 70.9%) than the control group participants (55.7%; 65.7%). This inferred that the participants in the intervention group considered themselves healthy.

Discussion: A correlation between the effects of IMT and re-intubation could not be confirmed. Inspiratory muscle strength improved for both groups, however no statistical difference was observed. Although PiMax had reportedly improved, the result cannot be attributed as a direct result of IMT. The initial intensity and progression of IMT training have been identified as limitations to this study. The use of IMT resulted in improved expiratory muscle strength. Results from the control group suggest that physiotherapy intervention alone results in improved overall muscle strength after critical illness.

Conclusion: The null hypothesis is supported by the results of this study. There was no statistical significance observed between the groups with regards to the improvement of inspiratory muscle strength. Physiotherapy intervention appears to play a vital role in the outcomes of patients recovering from critical illness.

ACKNOWLEDGEMENTS

- The University of the Witwatersrand for affording me the opportunity to conduct my research through their institution.
- The University staff at the Department of Physiotherapy, especially Professor Aimee Stewart and my supervisor Professor Heleen Van Aswegen for their constant support and guidance.
- The Faculty Research Council (FRC) grant for awarding me the grant.
- Charlotte Maxeke Academic Johannesburg Hospital Management.
- Charlotte Maxeke Academic Johannesburg Hospital, Physiotherapy department HOD, Miss Brenda Nyama and the physiotherapy staff members.
- The research assistants, Mrs Hannah Kim, Mrs Amrita Naidoo, Miss Hayley Macdonald, Miss Storm Bradbury and Miss Lindie Gerber for their willingness to take on more work and report back with such enthusiasm.
- The Medical ICU and high care staff, Sister Matshepo Moeti, Professor Guy Richards and Sister Cynthia Nhlapo, Surgical ICU and high care staff, Sister Mpilo Gcina, Professor Steve Moeng, and Sister Mercy Mashiane.
- Momentum Employee Benefits Team Leader, Leanie Schoeman and my colleagues.

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LIST OF ABBREVIATIONS

6MWT	: Six Minute Walk Test
ADL	: Activities of Daily Living
ALI	: Acute Lung Injury
ARDS	: Acute Respiratory Distress Syndrome
APACHE II	: Acute Physiology and Chronic Health Evaluation
BP	: Blood Pressure
CF	: Cystic Fibrosis
COPD	: Chronic Obstructive Pulmonary Disease
cmH ₂ O	: Centimetre of water
EQ-5D	: European Quality of Life 5-Dimension
GCS	: Glasgow Coma Scale
HAQ	: Health Assessment Questionnaire
HR	: Heart Rate
ICU	: Intensive Care Unit
ICU-AW	: ICU Acquired Weakness
ITT	: Intention to Treat
IMF	: Inspiratory Muscle Fatigue
IMT	: Inspiratory Muscle Trainer
KATZ	: Index of independence in Activities of Daily Living
LOS	: Length of Stay
MEP	: Maximal Expiratory Pressure
MIP	: Maximal Inspiratory Pressure
mmHg	: Millimeter of mercury
MV	: Mechanical Ventilation
NIF	: Negative Inspiratory Force
NMES	: Neuro-Muscular Electrical Stimulation
PEF	: Positive Expiratory Force
PeMax	: Maximal Expiratory Mouth Pressures
PiMax	: Maximal Inspiratory Mouth Pressures
PTSD	: Posttraumatic Stress Syndrome Disorder
QOL	: Quality of Life
RCT	: Randomised Control Trial
RR	: Respiratory Rate
SAPS II	: Simplified Acute Physiology Score II

SBT	: Spontaneous Breathing Trial
SPO ₂	: Peripheral Saturation of Oxygen
SOB	: Shortness of Breath
TV	: Tidal Volume
WOB	: Work of Breathing
VAS	: Visual Analogue Scale
VIDD	: Ventilator Induced Diaphragmatic Dysfunction

CHAPTER 1

1. INTRODUCTION

1.1 BACKGROUND

Patients who sustain a life-threatening illness, traumatic injury, acute exacerbation of chronic disease that leads to respiratory failure or who undergo emergency or routine complex surgery may need close monitoring and care in an intensive care unit (ICU). As a result of such patients' severity of illness or injury, they may develop critical illness (National Institute for Health and Care Excellence (NICE), Clinical Guideline (CG) 83, 2009; Khalil et al., 2012). The immune system responds to injury or trauma by activating inflammation that aims to protect the tissues from further damage and remove or destroy harmful agents to aid in the repair process.

A controlled amount of pro-inflammatory and anti-inflammatory cytokines are released into the blood circulation after any type of injury or inflammation and the balance in cytokine activity is restored within a reasonable amount of time in healthy individuals; however, an imbalance between pro-inflammatory and anti-inflammatory cytokine activity develops during critical illness, resulting in excessive tissue and cell damage (Rahman and McNee, 2000; Winkelman et al., 2007). The presence of reactive oxygen species (ROS) is part of the normal process and is produced during the inflammatory defence mechanism, however it has been reported that during critical illness there is an increase in ROS which may result in oxidative stress and resultant cell injury and death (Crimi et al., 2006). It is further reported that the state of critical illness is characterized by the presence of excessive depletion of lean body mass due to inflammation and sepsis and by marked fluid retention (Reid et al., 2004). Research has concluded that this state often results in the disruption of respiratory, cardiovascular, gastrointestinal and neuromuscular system functions in the human body (Heyland et al., 2003; Reid et al., 2004; Gosselink et al., 2008).

The art of breathing is predominantly reliant on the respiratory system that is responsible for ventilation and the diffusion process which allows for gas exchange, making oxygen utilization possible (Fox, 2004). The respiratory system is dependent on certain aspects in order to optimally function and serve its purpose. The physical aspects of ventilation are namely compliance, elasticity and surface tension (Fox, 2004).

Intrapleural pressure is the pressure surrounding the lungs and it is the driving force that links respiratory muscle actions to the movement of air (McConnell, 2013). The elasticity of the lungs pulling inwards and the chest wall pulling outwards during inspiration maintain the intrapleural pressure (McConnell, 2013). During inspiration the diaphragm and external intercostal muscles contract resulting in increased thoracic and lung volumes and subsequent decrease in intrapulmonary pressure (Fox, 2004). Inversely, expiration occurs due to the relaxation of the muscles and the elastic recoil that allows for the decrease in lung volume and the subsequent increase in intrapleural pressure (Fox, 2004). Therefore, the diaphragm plays a vital role in the mechanics of ventilation as it is the generator of inspiratory force (Martin et al., 2013). However, when the proficiency of the respiratory system is imbalanced or it is unable to function optimally due to the effects of critical illness, intubation and the use of the mechanical ventilator (MV) is often considered (Chang et al., 2005; Gosselink et al., 2008; Martin et al., 2013; McConnell, 2013).

Chang et al. (2005) states that at least 39% of patients admitted into the ICU will require MV. Mechanical ventilation is used in critical care settings to aid the respiratory system to overcome respiratory failure that in turn assists the cardiovascular, neurological and muscular systems with improved oxygen supply (Gosselink et al., 2008). This is achieved by decreasing the overload on the respiratory muscles to aid ventilation (McConnell, 2013) and sustaining alveolar ventilation (Martin et al., 2013). During MV, the diaphragm, which is accustomed to negative pressures that are vital in activating the stretch-like stimulus, is now exposed to positive pressures which result in reduced diaphragmatic activity during MV (Petrof et al., 2010). This allows for reduced activity of the diaphragm, and a decrease in strength and endurance as the inspiratory muscles are now being moved passively during MV. Diaphragm weakness may also develop as a result of ICU acquired weakness (Bruton et al., 2002; Van Aswegen et al., 2011).

Twenty five percent of ICU patients will have difficulty in weaning from the ventilator resulting in weaning failure (Crossingham and MacNaughton, 2009; Cavallone and Vannucci, 2013). This has been attributed to the inspiratory muscle weakness and fatigue that is caused by prolonged MV. Although the major changes occur whilst the patient is still mechanically ventilated, the resultant inspiratory muscle weakness continues to persist even after the cessation of MV (Goldstone, 2002; Chang et al., 2005). The adverse effects of weaning failure transcend beyond the respiratory

system, and may result in the prevalence of oxygen toxicity and organ specific dysfunctions (Goldstone, 2002).

To liberate the patient from invasive MV, the artificial airway that was utilized to transport oxygen and thus aid ventilation would need to be removed by the act of extubation. The patient's inability to cope with breathing after the artificial airway has been removed is termed extubation failure (Goldstone, 2002; Cavallonne and Vannucci, 2013; Thille et al., 2013). Thille et al. (2013) reports that extubation failure will occur in 10 to 20% of patients in the critical care setting and this is identified by the need for re-intubation within 48 hours, 72 hours or one week after extubation (Goldstone, 2002; Thille et al., 2013).

Thus, weaning and extubation failure have been identified as the predominant complications of MV and critical care, resulting in increased LOS and the increased re-intubation rates (Goldstone, 2002; Cavallonne and Vannucci, 2013). Re-intubation results in a 25% to 50% increase in mortality especially if the extubation was unplanned (Thille et al., 2013). Furthermore, the delay in the reinstatement of the artificial airway and ventilator support has been reported to result in death within 48 hours (Thille et al., 2013). A debilitating and equally serious complication of re-intubation is ventilator acquired pneumonia (VAP), (Gidani et al., 2010; Menon et al., 2012). The presence of VAP further increases the morbidity and mortality rate (Gidani et al., 2010; Menon et al., 2012).

Bed rest is inevitable in critical illness due to patients' initial severity of illness and in a critical care setting because of use of medical instruments that are connected to the patient to aid in their recovery but which restricts mobility (Winkelman, 2009). Physical inactivity results in muscle atrophy as measured in healthy and critically ill adults and can occur after three to five days of bed rest (Winkelman, 2009). Van Aswegen et al. (2011) stated that in a 24 hour period, approximately two percent muscle mass is lost due to the catabolic effect associated with critical illness. A further 40% decrease in muscle strength of anti-gravity muscles has been reported after a week of immobility in ICU (Bourdin et al., 2010). Malnutrition as a result of critical illness and the administration of pharmacological agents such as corticosteroids in the care of these patients contribute to muscle protein breakdown and resultant muscle weakness (Heyland et al., 2003; Petrof et al., 2010). Therefore, critical illness, bed rest and MV result in immobility, general skeletal muscle weakness, decreased exercise tolerance, decreased respiratory muscle

strength and endurance and increased perception of dyspnoea (Skinner et al., 2008; Ambrosino et al., 2012).

Physiotherapy plays an important role in the management of critically ill patients (Gosselink et al., 2008; Stiller, 2013). The objectives of early rehabilitation in ICU are to optimise oxygenation and function of the pulmonary system, improve overall functionality and prevent long term disability. This is achieved by applying various treatment modalities that address not only the respiratory system but also the skeletal and cardiovascular systems (Gosselink et al., 2008; Skinner et al., 2008; Ambrosino et al., 2012; Stiller, 2013).

The inspiratory muscle trainer (IMT), also known as the Threshold® IMT, reportedly assists with increasing respiratory muscle strength and endurance through the conditioning of the inspiratory muscles with the application of resistance against inspiration through a spring situated inside the device (Respironics, 2000; Geddes et al., 2008). Patients with chronic respiratory diseases such as cystic fibrosis (CF) and chronic obstructive pulmonary disease (COPD) report improved respiratory muscle function and less respiratory muscle fatigue and dyspnoea when IMT is incorporated into their home exercise programmes (De Jong et al., 2001; Riera et al., 2001). The use of IMT for patients who are being weaned from prolonged MV is gaining popularity. Similarly, other researchers reported that IMT increased their patients' tidal volume and maximal inspiratory pressure (MIP) and in some cases decreased weaning time from MV (Cader et al., 2010; Condessa et al., 2013). Chang et al. (2005) conducted a study using the Threshold® IMT device on two chronic critically ill patients. Respiratory muscle training with IMT was incorporated into these patients' standard in-patient physiotherapy treatment regimens. Although only two patients participated in this case study, there was a significant increase and improvement of MIP by 234% (Chang et al., 2005). Literature which reports on the effects of IMT implemented immediately after extubation with regards to the re-intubation rate could not be found.

1.2 STATEMENT OF PROBLEM AND JUSTIFICATION FOR RESEARCH

From the information shared in the background section, it is clear that severity of illness or injury and the resultant increased duration of immobility, malnutrition and drugs received in ICU result in generalised muscle weakness. As a consequence, the process of weaning from MV is longer for some patients and results in a longer ICU LOS. The effects of critical illness transcend beyond the patient's liberation from MV

as the resultant skeletal muscle weakness affects the patient's ability to resume their ADL's after discharge and negatively impacts their QOL (Elliot et al., 2011; Oeyen et al., 2012). The addition of the Threshold® IMT device to the rehabilitation of patients with chronic respiratory diseases seems to be beneficial in reducing their sensation and perception of dyspnoea and increasing their perceived level of QOL (Riera et al., 2001). The effect of training of the inspiratory muscles in addition to standard in-hospital physiotherapy treatment, initiated after extubation for patients who were on prolonged MV has not been investigated in relation to its effect on the patient's re-intubation rate, ability to participate in ADL, exercise endurance and their QOL during and after hospitalisation.

1.3 RESEARCH QUESTION

Would the use of IMT in addition to standard physiotherapy in-hospital treatment improve the outcomes of patients who underwent prolonged MV, after extubation?

1.4 SIGNIFICANCE OF RESEARCH

The research was conducted at a quaternary hospital in Johannesburg. Standard in-hospital physiotherapy intervention for patients who are recovering from critical illness after prolonged MV at this hospital involves clearance of excessive secretions from the pulmonary system, improvement of lung volumes and lung compliance, strengthening of peripheral muscles, mobilisation and improvement of exercise endurance but does not include inspiratory muscle training. A patient in this unit is generally deemed fit for hospital discharge when they can climb two flights of stairs on their own. Currently there are no structured outpatient rehabilitation programmes at this hospital for patients who are recovering from critical illness even though evidence shows that many survivors of critical illness still report reductions in QOL several months after discharge. If the addition of the Threshold® IMT device to the standard in-hospital physiotherapy programme for patients recovering from critical illness has a beneficial influence on patient outcomes in relation to maximal inspiratory (PiMax) and maximal expiratory mouth pressures (PeMax), re-intubation rate, perceived level of dyspnoea, participation in ADL, cardiovascular endurance and QOL, it can be recommended to form part of the standard physiotherapy in-hospital rehabilitation of such patients in the future.

1.5 RESEARCH AIM

To establish the effect of the addition of IMT to standard in-hospital physiotherapy treatment on the outcomes of patients who are extubated after prolonged MV.

1.6 RESEARCH OBJECTIVES

- a) To determine the baseline values for reintubation rate, PiMax and PeMax, perceived level of shortness of breath (SOB), participation in ADL, cardiovascular endurance and QOL in patients who are extubated after prolonged MV.
- b) To compare the rate of re-intubation after extubation at the time of hospital discharge between patients who had IMT plus standard in-hospital physiotherapy treatment programme and those who received a standard in-hospital physiotherapy treatment programme only.
- c) To compare the changes in PiMax and PeMax, perceived level of SOB, participation in ADL, cardiovascular endurance and QOL between patients who had IMT plus a standard in-hospital physiotherapy treatment programme and those who received a standard in-hospital physiotherapy treatment only as measured at the time of hospital discharge, one month and three months after discharge respectively.

1.7 TYPE OF STUDY

To ascertain the plausibility of the outlined objectives, a single-blinded randomised controlled trial (RCT) was conducted.

The following chapter will consist of the review of literature pertaining to respiratory system anatomy and physiology and how these are influenced by MV; the effects of critical illness on peripheral and respiratory muscle function and its effects on weaning of patients from MV; causes of extubation failure and consequences of re-intubation on patient outcome; physiotherapy involvement in the care of critically ill patients; diaphragmatic strength measurements in the form of PiMax and PeMax in clinical practice; the use of IMT in different patient populations will be explored and how this could influence cardiovascular endurance, ADL and QOL in patients recovering from critical illness.

CHAPTER 2

2. LITERATURE REVIEW

This literature review was conducted in order to ascertain the evidence that is available on the adverse effects of prolonged mechanical ventilation, muscle wasting and prolonged bed rest in critically ill patients; the use of IMT in patients who are mechanically ventilated and after extubation; the effects of IMT on QOL, ADL, cardiorespiratory endurance and shortness of breath in patients who were previously intubated, mechanically ventilated and are now extubated. Journal articles written in the English language and published between the 1996 to 2015 period were reviewed. The search engines used in order to conduct this review were Science Direct, PubMed, EBSCO host, SCOPUS, Biomed Central, The Cochrane Library and MedlinePlus. Keywords that were used to source information included: inspiratory muscle training and physiotherapy; inspiratory muscle training and critical illness; critical illness and inspiratory muscle training; inspiratory muscle training in ICU; QOL and critical care; ADL and critical care; physiotherapy in ICU; IMT in ventilated patients; HIV and ICU; critical illness and nutrition.

2.1 RESPIRATORY SYSTEM

The respiratory system is made up of a respiratory and a conducting zone. The anatomical makeup of the respiratory system branches out from the trachea, bronchi and bronchioles creating a tree like structure. This segment of the system is known as the conducting zone and it is responsible for the conduction of air to the respiratory zone. Following the conduction process, gaseous exchange occurs in the respiratory zone which is made up of the intricate network between the alveoli and capillary system (Fox, 2004; McConnell, 2013).

2.1.1 Ventilation and Immune Response

Boyle's law suggests that for breathing to occur there should be maintenance of a constant pressure and volume in the lungs (Sandham, 2005; McConnell, 2013). The small negative pressure surrounding the lungs is known as intrapleural pressure. If the atmospheric pressure is more than the intrapleural pressure, inspiration would occur. Expiration occurs because the atmospheric pressure is less than the intrapleural pressure (Ratnovsky et al., 2008; McConnell, 2013). Air easily moves from a higher concentration outside of the lungs, into the lungs when the intrapleural pressure is slightly negative. The contraction of the diaphragm results in inspiration

and expiration occurs when the diaphragm relaxes (Sandham, 2005). There are other factors that play a vital role in the mechanism of breathing, such as the ease of air through the bronchioles known as airway resistance, the ability of the lung to recoil at expiration known as lung elasticity and the ability of the alveolae to expand during inspiration known as lung compliance (Sandham, 2005).

The purpose of MV is to unload the inspiratory muscles and to decrease work of breathing (WOB) whilst optimising ventilation and gaseous exchange (Jubran, 2006; Sandham, 2005). Mechanical ventilation applies positive pressure ventilation to the lungs, meaning that the pressures that are normally kept slightly negative are now positive (Sandham, 2005). The diaphragm is not challenged to perform but rather to conform to the force generated by the MV (Jubran, 2006). This, however predisposes the inspiratory muscles to ventilator induced diaphragmatic dysfunction (Jubran, 2006). Other observed and researched side effects of MV include barotrauma, oxygen toxicity, volutrauma and biotrauma (Slutsky, 2013). Biotrauma occurs as a response to mechanical stresses, the lung releases mediators within its tissues that are meant to protect but result in further damage of the lung tissue (Slutsky, 2013). This occurs because the lungs react to the act of intubation and MV as any other organ would to invasion or infection (Ghadiali and Nana-Sinkam, 2012). The use of MV results in increased diaphragmatic oxidative stress caused by reactive oxygen species (ROS) and reactive nitrogen species (RNS) (Falk et al., 2006). These processes are normally controlled in healthy subjects by the presence of anti-oxidants. However, during MV and critical illness the patient already has decreased intracellular plasma and anti-oxidants; therefore anti-oxidant imbalance is inevitable (Abilés et al., 2006). The increase in ROS results in cell injury and apoptosis (Crimi et al., 2006). Mechanical ventilation further incites lung injury by releasing inflammatory mediators, cytokines and chemokines. Pro-inflammatory markers such as IL-1, IL-6, oxidants, nitric oxide and TNF- α (tumour necrosis factor alpha) have been reported to result in multi-organ failure and death (Abilés et al., 2006; Cox, 2012; Sun et al., 2014). This occurs because the anti-inflammatory markers such as IL-4 and IL-10 are unable to maintain the balance between the pro and anti-inflammatory processes. Proteolysis occurs through the ubiquitin pathway, calpase and the lysosomal and non-lysosomal which involves the degradation of cells (Cox, 2012). This augments the effects of critical illness and immobility, which result in an increased catabolic process, which outweighs the anabolic process regardless of nutritional supplementation (Bruton et al., 2002; Powers et al., 2009; Winkelman et al., 2009;

Dos Santos and Batt, 2012; Martin et al., 2013). Thus, predisposing the patient to compounded muscle mass loss and weakness (Winkelman et al., 2009). The inflammatory, anti-oxidant imbalances and the proteolytic process are well established processes that occur during critical illness, MV and the subsequent lung injury (Cox, 2012). Some researchers have inferred that positive ventilation may affect the lymphatic drainage system, as it may not drain excess fluid as well as the use of negative pressures (Soni and Williams, 2008). This would result in the impaired production and dysfunction of surfactant due to the increase in circulating protein (Soni and Williams, 2008). The cumulative effects of critical illness and the exaggerated cellular immune response are likely to impose a challenge when weaning and extubation are considered (Cox, 2012). This is due to the fact that the lungs are in a constant state of injury and will therefore continue activating inflammatory responses that further destroy the lung tissue (Ghadiali and Nana-Sinkam, 2012).

2.1.2 Weaning and Extubation of Patients from MV

The factors that may affect the weaning process include malnutrition which has adverse effects on the respiratory system, infection, ventilator acquired infection, ventilator induced diaphragmatic dysfunction (VIDD), and critical illness oxidative stress (Khalil et al., 2012). Furthermore, inadequate respiratory drive, muscle weakness and fatigue, increased work of breathing and cardiac failure also affects the weaning process (Gayan-Ramirez and Decramer, 2002). The use of spontaneous breathing trials (SBT) and decreasing ventilatory support have been identified as objective measures that determine if a patient is ready for extubation (Carpene et al., 2012). Numerous weaning protocols such as nurse-driven and physiotherapy-driven protocols are utilized as tools to prepare for extubation (Bissett et al., 2012; Carpene et al., 2012; Plani et al., 2013). However, these protocols merely look at the patient's ability to cope without ventilatory support as opposed to evaluating the ability of the respiratory muscles. Nemer et al. (2009) proposed that diaphragmatic strength be evaluated in patients at risk of weaning failure. The positive inspiratory maximum (PiMax) and the positive expiratory pressure (PeMax) are measurements used to measure direct diaphragmatic strength (Evans and Whitelaw, 2009; Khamiees et al., 2011). The PiMax in normal subjects is reported as -104 to -129 cmH₂O in men and -70 to -98 cmH₂O in women (Nemer et al., 2009; Moodie et al., 2011). Nemer et al. (2009), suggests that a PiMax range of -20, -25 and -30 cmH₂O could be an indicator for successful weaning (Nemer et al., 2009). The PeMax in healthy subjects has been reported as ≤ 50 cmH₂O with the median value accepted as 30 cmH₂O (De

Jonghe et al., 2007). Currently literature has not identified quantifiable Pe_{Max} ranges that may serve as reference for weaning success (De Jonghe et al., 2007). The procedure of terminating ventilation involves the cessation of mechanical ventilation and the preparation of the removal of the artificial airway (Su et al., 2010). Premature extubation occurs and results in further complications and increases mortality and morbidity (Plani et al., 2013). Thille et al. (2013) states that 50-60% of extubations are planned, with 5-15% being accidental. Mortality is increased by 25-50% due to the occurrence of accidental or unplanned extubations (Thille et al., 2013). The direct correlation between mortality and extubation has not yet been defined, however it has been reported to be due to the delay in re-intubation, multi organ failure and the trauma involved with re-intubation (Seymour et al., 2004; Thille et al., 2013).

Following the careful planning of extubation, 10-20% of patients will still fail extubation (Seymour et al., 2004; Thille et al., 2013). Patients who fail extubation usually have a decreased Glasgow Coma Scale (GCS) score, reduced cough strength due to respiratory muscle weakness, which results in secretion retention and the inability to clear retained secretions (Cavallonne and Vannucci, 2013; Thille et al., 2013). This will then give rise to other complications such as pneumonia, lobar collapse and respiratory distress which might require the re-institution of MV (Seymour et al., 2003; Thille et al., 2013). Boles et al. (2007) and De Wit et al. (2009) stated that the need for re-intubation occurs when a patient is unable to cope without invasive ventilation within 48 or 72 hours of extubation. Although respiratory muscle strength has been noted as a factor resulting in the need for re-intubation, other factors such as upper airway obstruction, stridor, decreased GCS and the inability to clear secretions by coughing also contribute to the need for re-intubation (Goldstone, 2002; Thille et al., 2013).

2.2 REASONS FOR ADMISSION TO ICU

2.2.1 Respiratory Failure

2.2.1.1 Compromised airway

There is a high incidence of unnatural causes of death in South Africa which result from activities of crime such as theft, hijacking or assault (Van Aswegen et al., 2011). The injuries sustained may result in some victims' airways being threatened, thus the most effective emergency intervention is the method of airway protection by intubating such patients (Martin-Loeches et al., 2013; Slutsky et al., 2013). Other patients may have an inability to cough effectively due to numerous factors such as postoperative pain, inspiratory and expiratory muscle weakness and neurological

impairments; thus predisposing the airway to increased amounts of secretions that end up obstructing the upper airway and thus compromising ventilation (Volpe et al., 2008; Ambrosino et al., 2012). This may further lead to the complication of atelectasis and increases the chances for the development of nosocomial pneumonia (Volpe et al., 2008; Ambrosino et al., 2012). Emergency situations also occur in cases where the patient aspirates and a need arises to protect the airway and optimise ventilation (Thille et al., 2013).

2.2.1.2 Acute infections

Methicillin-resistant staphylococcus aureus, pseudomonas aeruginosa, ESBL-producing bacteria and candida have been reported to account for five percent of sepsis in critically ill patients (Tupchong et al., 2014). The resultant infection caused by some of these bacterial strains may result in chest infections that increase the production of airway secretions and hinders the patient's cough effort (Ambrosino et al., 2012; Tupchong et al., 2014). Akgün et al. (2011) classifies medical conditions that often require ICU admission as *Pneumocystis jiroveci* pneumonia (PJP), bacterial pneumonia which often results in respiratory failure and other respiratory diseases such as interstitial pneumonitis and lymphocytic interstitial pneumonitis. Four to twelve percent of patients with HIV who are admitted to the hospital have been reported to require ICU admission for the management of opportunistic infections such as PJP and pulmonary tuberculosis (PTB) (Akgün et al., 2011; Shosbree et al., 2013). Akgün et al. (2011) further reports that the prevalence of respiratory failure and the need for MV amongst patients with HIV has become the main reason for ICU admission.

2.2.1.3 Exacerbation of chronic diseases

The immune systems of patients living with chronic diseases is already compromised, therefore the acute exacerbation of chronic obstructive pulmonary disease (COPD) and asthma, cardiac conditions, and renal dysfunction may result in respiratory failure and may lead to the requirement of intubation and possibly prolonged MV (Akgün et al., 2011; Loss et al., 2013). The respiratory muscles in chronic respiratory diseases are placed under chronic overload, which is worsened by an acute exacerbation (McConnell, 2013). Ineffective triggering of the MV occurs in 80% of patients with COPD who are mechanically ventilated and creates asynchrony which may result in the prolonged use of the MV (de Wit et al., 2009). The presence of decreased respiratory muscle strength, respiratory drive specifically due to sedation and increased dynamic hyperinflation may encourage ineffective

triggering of the MV (de Wit et al., 2009), thus predisposing the respiratory muscles to injury and fatigue (de Wit et al., 2009). Numerous non-respiratory chronic conditions can result in the need for MV. Akgün et al. (2011) states that 80% of neurological conditions that manifest in 20% of the HIV cases require MV. Akgün et al. (2011) further reported that the development of complications such as immune reconstruction inflammatory syndrome (IRIS) in patients who are HIV positive usually manifests as an autoimmune disease and would often result in respiratory failure.

2.2.1.4 Sepsis and acute lung injury

Sepsis accounts for 41.3% of the cases in ICU (Martin-Loeches et al., 2013). The systemic response that results from the interaction of microbes and the immune system, results in a downstream inflammatory cascade involving cytokines and other mediators that may result in the development of sepsis (Tupchong et al., 2014). Dellinger et al. (2008) defines sepsis as 'an infection plus systemic manifestations of infection.' Severe sepsis is defined as sepsis plus sepsis induced organ dysfunction or tissue hypoperfusion and septic shock is defined as 'sepsis induced hypotension that persists even after fluid resuscitation' (Dellinger et al., 2008). Fluid resuscitation, inotrope therapy, bicarbonate treatment, steroids, vasopressors, antibiotic therapy, sedation and analgesia are among the vast treatment modalities that are administered to patients who are diagnosed with sepsis (Dellinger et al., 2008; Tupchong et al., 2014). The diagnosis of sepsis often results in acute lung injury (ALI) and acute respiratory distress syndrome (ARDS), (Seeley, 2013). Due to the high susceptibility of developing ARDS/ALI in the case of sepsis, MV therapy aims to decrease work of breathing (WOB), optimise ventilation and perfusion (Chang et al., 2005), protect the diaphragm from sarcolemma injury induced by sepsis (Gayan-Ramirez and Decramer, 2002) and treat respiratory failure (Ely et al., 2004). Tidal volumes (TV) of less than 6ml/kg with plateau pressures less than 30 cmH₂O, also known as lung protective ventilation, have been reported to decrease patient mortality rate and protect the lungs from further injury (Girard and Bernard, 2007; Seeley, 2013). The development of ARDS also predisposes patients to acute kidney infection, which increases patient mortality rate to 60% as opposed to 28% mortality in ARDS alone (Seeley, 2013). The involvement of kidney impairment further increases the pulmonary neutrophil accumulation and capillary permeability resulting in a further increase in circulating inflammatory cytokines (Seeley, 2013). Interleukin-6 (IL-6) circulation is increased in kidney dysfunction and as a result it is known to mediate lung injury (Seeley, 2013). This process hampers the ability of the kidneys in the removal of solute and water from the alveoli (Seeley, 2013). Therefore in these

cases, the administration of MV serves as an anti-inflammatory agent and has a cytoprotective effect on the diaphragm muscle (Seeley, 2013).

2.3 THE EFFECTS OF CRITICAL ILLNESS AND MV ON MUSCLE TISSUE

2.3.1 Physiology of Peripheral and Respiratory Muscles

Critical illness has been associated with marked skeletal muscle mass loss, this has been attributed to age, immobility, nutrition, inflammation, the use of neuromuscular blocking agents, sedatives and steroid medication (Helliwell et al., 2002; Puthuchearry et al., 2010; Puthuchearry et al., 2013). The skeletal muscle fibres are classified into types. Type 1 is the slow twitch muscle fibre; type 2A is moderately fast, strong contraction with high resistance to fatigue and lastly type 2B which is very fast and contracts strongly with moderate resistance to fatigue (McConnell, 2013). The diaphragm and the inspiratory muscles consist of 80% of type 1 and 2A fibres whereas the limb muscles only contain 35-45% of these fibres (McConnell, 2013). Types 1 and 2A are the oxidative fibres and are able to sustain activity for prolonged periods without fatiguing (McConnell, 2013). During the process of critical illness, type 1 and 2A fibres undergo structural changes which result in fibre loss in locomotor muscles, myofibrillar disorder in the diaphragm and Z-line structural changes in both the locomotor and diaphragm muscles (Díaz et al., 2014). In healthy subjects protein catabolism is balanced by anabolism but this may not be the case in critical illness (Puthuchearry et al., 2010). Malnutrition is a state resulting from increased observable catabolic hormones such as glucagon, adrenaline and cortisol. This state often results in hypermetabolism, which in turn attenuates muscle mass loss, strength and immune response (Winkelman et al., 2007; Díaz et al., 2014). Caspase and calpain pathways are proteolytic enzymes that accelerate the ageing denervation, and induce atrophy and muscle proteolysis (Bruton et al., 2002; Powers et al., 2009; Dos Santos and Batt, 2012; Martin et al., 2013). These pathways work in conjunction with the ubiquitin-proteasome pathway that has been reported to be responsible for signalling the atrophy gene. This usually occurs in states of prolonged immobility, inflammation and sepsis (Puthuchearry et al., 2010).

2.3.2 Factors Related to the Development of Peripheral Muscle Weakness

The duration spent in ICU or in a state of critical illness results in the reduction of gravitational and contractile forces on the skeletal system which further disrupts the mechanical compression of long bones during inactivity due to bed rest (Winkelman, 2009). Osteoclasts are bone destroying cells that are increased during the period of immobility (Winkelman, 2009). Orford et al. (2014) states that critical illness increases

bone turnover and that inevitably results in osteoporosis. A length of stay (LOS) of five days in ICU and inflammation increases bone turnover, which may result in fractures thus increasing the morbidity and mortality rate in some patients specifically the elderly and menopausal females if not identified and treated accordingly (Orford et al., 2014). Patient immobilisation results in alteration of the skeletal morphology which leads to a disproportion between slow and fast twitch fibres, disturbs muscle contractility, decreases muscle protein synthesis which result in decreased muscle strength and increases the likelihood of fatigue (Puthucheang et al., 2010). Crossingham and MacNaughton (2009) report that on average two percent of muscle wasting occurs per day in patients on prolonged MV, with a further 40% muscle loss in antigravity muscles after a week in ICU (Bourdin et al., 2010). Furthermore, prolonged bed rest and immobility is directly correlated with the development of atrophy, resulting in weakness and fatigability of peripheral muscles (Skinner et al., 2008; Winkelman, 2009). A report states that adequate nutritional supplementation does not counter the effects of critical illness on skeletal mass depletion (Reid et al., 2004). The peripheral muscles do not function independently and are reliant on the optimal functioning of the respiratory system. The modulation of blood flow between the respiratory and working locomotor muscles is controlled by the inspiratory muscle metaboreflex (Chiappa et al., 2008; McConnell, 2013). Therefore, increased WOB and the inability of the respiratory muscles to cope with the increased load will result in further decreases in exercise tolerance and blood flow to the locomotor muscles (McConnell, 2013).

2.3.3 Factors Related to the Development of Respiratory Muscle Weakness

Prolonged unloading of respiratory muscles during MV results in prominent respiratory problems such as reduction of inspiratory muscle force, changes in total lung capacity and compliance and increased residual volume (Enright et al., 2004; Chang et al., 2005). These changes may result in hypoventilation, hypoxemia and acute infections therefore hindering the process of weaning, prolonging MV duration and encouraging the development of complications such as lobar collapse (Stein et al., 2009; Castro et al., 2013).

Extensive studies of animal and human models have been conducted to evaluate the extent of diaphragmatic atrophy, injury and the resultant reduced endurance and strength during and after the use of MV. The results may vary with regards to whether strength is more compromised than endurance; however the studies concur on the fact that the duration of MV ranging from 18 hours to 48 hours and more will

result in structural and functional changes of the diaphragm resulting in the prolonged use of MV (Gayan-Ramirez and Decramer, 2002; Chang et al., 2005; Petrof et al., 2010; Khalil et al., 2012; Condessa et al., 2013; Martin et al., 2013). Díaz et al. (2014) further states that atrophy of slow and fast twitch fibres occurs in 12-18 hours on MV in animal studies and in humans diaphragm atrophy ensued after 18-69 hours of MV. Furthermore, the weight of the diaphragm decreased more than the weight of peripheral muscles because of atrophy and fast twitch fibre remodelling (Diaz et al., 2014). The imbalance that occurs between strength and the load of respiratory muscles results in a demand and capacity imbalance that results in diaphragmatic dysfunction (Ambrosino et al., 2012; McConnell, 2013). Dysfunction of the diaphragm may result in ventilation failure because the respiratory system is working beyond its mechanical limits and has been deconditioned (Gayan-Ramirez and Decramer, 2002; Karakurt et al., 2012). This may result in the incidence of inadequate ventilator drive, increased WOB, cardiac failure and inspiratory muscle weakness and could predispose a patient to VIDD (Bruton et al., 2002; Powers et al., 2009; Dos Santos and Batt, 2012; Martin et al., 2013). Martin et al. (2013) observed the effect of MV in animals ventilated for 6-24 hours and deduced that in one week 6% of diaphragmatic thickness had decreased and this was because of an increased muscle fibre proteolysis, which decreased the contractile force. In humans excessive atrophy and proteolysis occurs in the respiratory muscles as compared to other skeletal muscles as a result of prolonged MV (Ambrosino et al., 2012). Other factors such as the use of anaesthesia predisposes the respiratory system to complications such as atelectasis, infection and result in a statin induced myopathy (McConnell, 2013). The site of the surgery also plays a vital role, abdominal or thoracic surgery is believed to encourage chest wall immobility thus inducing thoraco-abdominal and respiratory muscle dysfunction. Post-operative pain also results in impaired respiratory muscle function (McConnell, 2013). An important factor in muscle performance that has not always been clearly described is fatigue. It is acknowledged that where muscle excitability occurs, fatigue may limit the performance (McConnell, 2013). Fatigue is defined as 'an acute impairment of performance that includes both an increase in the perceived effort necessary to exert a desired force and an eventual inability to produce this force' (McConnell, 2013). Chang et al. (2005) defines central fatigue as the 'reduction in voluntary contraction force due to reduced central nervous system (CNS) output and peripheral fatigue occurs when the contractile component of the muscle or neuromuscular junction fails'. Meeusen et al. (2006) states that central fatigue is associated with the level of serotonin and dopamine, thus the increase of these levels may result in feelings of tiredness and lethargy thus accelerating the

onset of fatigue. Peripheral fatigue is encountered when oxygen delivery to the locomotor muscles is influenced due to the inability to meet the demand thus increasing the development of dyspnoea as a result of the resultant inspiratory muscle weakness (McConnell, 2013) and inspiratory muscle fatigue (Chang et al., 2005).

2.4 EARLY PHYSIOTHERAPY INTERVENTION IN ICU

2.4.1 Principles of Physiotherapy in ICU and Physiotherapy Treatment Modalities

Clark and Lettieri (2013), state that 3-14% of patients admitted into the ICU will require prolonged MV and that 25% of the patients mechanically ventilated for more than seven days will have prolonged weakness inferred by immobility, disuse atrophy, prolonged MV, systemic infection and inflammation (Skinner et al., 2008; Condessa et al., 2013). ICU-acquired weakness (ICU-AW) has been reported in 50% of patients who are mechanically ventilated for longer than seven days (Puthuchearry et al., 2010). The resultant disability that occurs after critical illness due to muscle wasting and weakness is evident five years after discharge (Puthuchearry et al., 2013). The physical changes that occur in patients are due to muscle wasting resulting in muscle weakness and breathlessness due to reduced physical function (Kelly and McKinley, 2010). The impediment of function and long-term disability are some of the consequences of critical illness (Skinner et al., 2008; Van Aswegen et al., 2011). Resistance training of the limb exercises and inspiratory muscles are prescribed by physiotherapists with the aim of increasing strength and decreasing the weaning time in patients who are mechanically ventilated (Ambrosino et al., 2012).

Early initiation of rehabilitation is reported to improve the physical and functional status of the patient and decrease ICU-LOS (Thomas, 2011; Rodriguez et al., 2012; Castro et al., 2013; Hill et al., 2013). Numerous treatment techniques are adopted by physiotherapists in order to reduce intrapulmonary shunt and increase compliance in patients on MV (Castro et al., 2013) and to increase respiratory and general muscle strength in intubated and extubated patients (Skinner et al., 2008; Ambrosino et al., 2012). Respiratory therapy becomes a focal point of physiotherapy in ICU with the aim of improving ventilation and perfusion (V/Q) mismatch, optimising ventilation and preventing secondary respiratory complications (Gosselink et al., 2008). Manual chest therapy comprising of percussions, vibrations and shakes has been used in conjunction with postural drainage to assist in the loosening and clearance of airway secretions. Administering these techniques has been reported to result in a 31% decrease in the risk for development of ventilator associated pneumonia (Clini and

Ambrosino, 2005). Airway suctioning is performed to assist the patient to clear retained secretions and manual cough assistance techniques are also practiced to induce a cough effective enough to clear secretions in patients who are unable to cough actively and effectively (Gosselink et al., 2008; Ambrosino et al., 2012; Nordon-Craft et al., 2011). Deep breathing exercise techniques such as active cycle of breathing (ACBT) are incorporated in routine treatment sessions and are taught to patients. This technique facilitates movement of secretions from peripheral to central airways and to improve lung capacity and volume (Ambrosino et al., 2012). Manual hyperinflation has been reported to prevent pulmonary collapse, re-inflate collapsed alveoli, mobilise secretions to the central airways, improve oxygenation and ventilation as well as static and dynamic lung compliance (Gosselink et al., 2008; Skinner et al., 2008; Nordon-Craft et al., 2011; Ambrosino et al., 2012; Jacobs, 2013). Gosselink et al. (2008) reports that the practice of these techniques may result in a decrease in LOS and ultimately minimize cost. Castro et al. (2013) concurs that the practice of chest physiotherapy results in decreased LOS, MV days, chest infection and mortality rates. Skinner et al. (2008) states that most physiotherapists prescribe bed based exercises with the aim of increasing endurance, strength, range of motion and function for patients on MV. Passive, active, active-assisted and resisted exercises are often prescribed to assist in the prevention of joint and muscular dysfunctions and maintain the length and strength of the skeletal muscles (Nordon-Craft et al., 2011; Ambrosino et al., 2012). Neuromuscular electrical nerve stimulation (NMES) is a low volt stimulator that elicits muscle contraction and can be used in conjunction with the bed exercises (Ambrosino et al., 2012). It aims to slow down the rate of muscle mass loss and strength (Clini and Ambrosino, 2005; Ambrosino et al., 2012). Although it has been proven to be useful in other chronic conditions there is little evidence proving its effectiveness on exercise tolerance in patients recovering from critical illness (Clini and Ambrosino, 2005). Mobilisation is one of the standard physiotherapy interventions prescribed for critically ill patients and is an umbrella term that encompasses various activities (Thomas, 2011). Standing after abdominal surgery has been reported to increase the minute volume by 41% and the TV by 24%, whilst the use of a tilt table improves the minute volume by 27% and the TV by 17% (Thomas, 2011). Sitting at the edge of the bed, sitting in the chair, the use of the standing frame and cycle ergometry are some of the interventions that are routinely prescribed to patients in ICU (Thomas, 2011). Gosselink et al. (2008) reports that a six week upper and lower limb aerobic and muscle strengthening programme improves muscle strength, functional outcomes and resulted in an increase of ventilator free days in patients requiring long term

ventilation. The introduction of resistive muscle training has been reported to increase muscle mass and oxidative enzymes which in turn improve oxygen delivery to the peripheral muscles (Skinner et al., 2008). Thomas (2011) states that if a comprehensive rehabilitation programme is implemented, there is a 120% improvement in the distance walked during the 6MWT at hospital discharge. Therefore, cardiovascular training is an important factor in exercise physiology (McConnell, 2013). The principles of cardiovascular training are to create an overload that evokes muscle or system adaptations. The effects of training on the skeletal and respiratory muscles induce increased blood flow, reduced lactic acid production and decrease in oxygen cost (McConnell, 2013). Therefore it is essential that exercise should overload the lactate clearance mechanism in order to produce changes that would result in improved functional outcomes (McConnell, 2013). The importance of the addition of respiratory muscle training as part of standard physiotherapy care for critically ill patients has been mentioned in numerous articles, as a facilitator for weaning or to improve the inspiratory muscle strength (Ambrosino et al., 2012; Condessa et al., 2013; Martin et al., 2013). However, there are few reports on the effects of this specific training after critical illness (Chang et al., 2005).

2.5 INSPIRATORY MUSCLE TRAINING

The objective of the IMT is to provide a constant, specific, measurable resistance throughout each breath on inspiration, thus initiating a strengthening stimulus and encouraging neuromuscular changes (Chang et al., 2005; Moodie et al., 2011; Bisset et al., 2012; Condessa et al., 2013). The training stimulus of IMT is specific in that it results in increased muscle length and improves endurance by increasing strength through low load frequency contractions (McConnell, 2013). The implementation of such a programme would result in improved muscle mass of the inspiratory muscles by hypertrophy, therefore it is surmised that this may reverse or delay the complications of impaired inspiratory muscle fatigue (Chiappa et al., 2008; Petrovic et al., 2009; McConnell, 2013). The diaphragm, just like any other skeletal muscle, responds to the training principles of overload, specificity and reversibility (McConnell, 2013). By creating an overload, a training effect is created and it increases the type 1 and 2 muscle fibres of the diaphragm muscles and reduces lactate production (Riera et al., 2001; Bisset et al., 2012). Diaphragmatic muscle thickness is increased by 8 to 12% after four weeks of IMT in healthy individuals. McConnell and Griffiths (2010) confirmed that using IMT would result in improved exercise tolerance in healthy young athletes as well as patients with respiratory and cardiovascular disease. De Jong et al. (2001) reports further on this phenomenon,

that through the independent use of IMT, muscle strength increased and there was reduced sensation of inspiratory effort in healthy subjects, thus proving that the benefits of IMT transcend beyond the ill patient. These results were achieved by initialising treatment at 30% of MIP and increasing it by 20% throughout the treatment period (McConnell, 2013). After six weeks of maintaining an average of 30% of MIP, pulmonary function had improved and a decreased perception of breathlessness was noted (Riera et al., 2001; De Jong et al., 2001). In chronic respiratory conditions such as chronic obstructive pulmonary diseases (COPD) and cystic fibrosis (CF) specific IMT delays inspiratory muscle fatigue and therefore delays dyspnoea and more specific tests such as 6MWT improved after the IMT intervention (De Jong et al., 2001; Shoemaker et al., 2009). There are numerous ways to administer IMT intervention in intubated patients; some studies reportedly used the isocapnic hyperpnea method (Patsaki et al., 2013) or the manipulation of the trigger sensitivity (Caruso et al., 2005) of the MV. However, for the purposes of this study, we will report on studies that made use of the Threshold® IMT device.

2.5.1 Inspiratory Muscle Training in Intubated Patients

Inspiratory muscle training in ventilated patients has been investigated and reported on since the 1980's (Patsaki et al., 2013). Currently studies by Bissett et al. (2012) and Patsaki et al. (2013) report that successful weaning is attainable after an IMT programme is implemented. These studies report on programmes that were administered to patients diagnosed with stable chronic respiratory failure and ventilator dependant tracheotomised patients that had repeatedly failed weaning trials (Bissett et al., 2012; Patsaki et al., 2013).

Varied methods of training have been studied. Some researchers used the low intensity and longer duration method (Cader et al., 2010; Condessa et al., 2013). The initial training load was set at 30% of PiMax, this was increased by 10% at each session. These sessions were administered twice a day for five minutes. The results of such a training method resulted in an increase of MIP by 7.6 cmH₂O and reduced the weaning period (Cader et al., 2010).

The other form of training relied on the method of high intensity with a shorter duration. In one study conducted on medical and surgical patients, the training was initiated at 50% of PiMax or the highest tolerable pressure. This was administered five days of the week, for four sets of six to ten breaths (Martin et al., 2011; Bissett et al., 2012), thus, resulting in 71% of the participants being successfully weaned from

MV (Martin et al., 2011) and an improvement of MIP of between 11 to 31.5 cmH₂O (Martin et al., 2011; Bissett et al., 2012).

Therefore it can be said that the administration of IMT in patients intubated for acute respiratory failure, has resulted in the reduced duration of weaning from MV (Cader et al., 2010; Bissett et al., 2012; Patsaki et al., 2013), resulting in diaphragmatic muscle mass thickness increase by 10% and improving inspiratory muscle strength (Downey et al., 2007; Moodie et al., 2011). Literature has not yet reported on significant effects of IMT on weaning success; however, some studies support the use of IMT in reducing the weaning duration and re-intubation rate (Cader et al., 2012; Condessa et al., 2013; Patsaki et al., 2013).

2.5.2 Inspiratory Muscle Training after Extubation

It has been established that the effects of prolonged MV and critical illness result in reduced MIP, this continues even after successful weaning and discharge from ICU (Chang et al., 2005; Bisset et al., 2015). Currently not a lot of research has been done on the administration of IMT in patients who have been extubated following a period of MV.

Chang et al. (2005) set out to conduct a case report where IMT was administered in addition to standard physiotherapy treatment to two medical patients after ICU discharge. The treatment was administered twice a day by the therapist, the patients were instructed to do eight breaths and repeat three times. The programme was continued until the patients' discharge from the hospital (Chang et al., 2005). On assessment it was reported that there was significant improvement in MIP by 234%, an increased exercise endurance and performance on the ADL scale (Chang et al., 2005). However, not enough research is done to ascertain the effectiveness and need of an IMT programme for patients who have been liberated from the MV and are discharged from ICU (Chang et al., 2005).

2.6 PERCEPTION OF BREATHLESSNESS AND EXERCISE TOLERANCE AFTER THE SURVIVAL OF CRITICAL ILLNESS

The symptoms that arise from respiratory muscle dysfunction due to critical illness or prolonged bed rest include the perception of breathlessness known as dyspnoea and decreased exercise tolerance (McConnell, 2013). Dyspnoea is a subjective symptom that is normal to a certain extent during activities that induce overexertion, however it becomes a problem when it is experienced during normal activities or hinders activities of daily living (Nicholls, 2000; Thomas and von Gunten, 2002; McConnell, 2013). If one believes that they are unable to breathe and are conscious of the increase in respiratory effort, oxygen delivery to the loco motor muscles would be affected and there would be a decrease in exercise tolerance (McConnel, 2013). Elliot et al. (2011) found that although 89% of critically ill patients recover there was marked residual decrease in exercise endurance as measured with the 6MWT. When the 6MWT was applied after discharge from ICU in a study by Chang et al. (2005), the total distance measured in metres was zero. The resultant morbidity that occurs due to these symptoms would have an impact on the QOL and the ability to perform ADL's after discharge from ICU (Chang et al., 2005; Elliot et al., 2011).

2.7 QUALITY OF LIFE AND ACTIVITIES OF DAILY LIVING LIMITATIONS AFTER THE SURVIVAL OF CRITICAL ILLNESS

Modern medicine and sophisticated equipment have increased the survival rate of critically ill patients over the last few decades; the adverse effect of this success has been reported to result in the increased morbidity of survivors of critical illness at twelve months after discharge (Hill et al., 2013) and the residual disability (Latronico and Bolton, 2011).

Research alludes to the fact that pre-admission health related quality of life (HRQOL) reduces in patients who were admitted into the ICU for 48 hours and more, this state continued at one, three and six months after discharge respectively from ICU after prolonged MV (Hofhuis et al., 2008; Van Aswegen et al., 2011). Emotional and mental health are vital aspects that often get overlooked in patients recovering from critical illness. Anxiety, depression and posttraumatic stress syndrome disorder (PTSD) have been identified as the most predominant psychological problems that may arise during the recovery from prolonged critical illness (Rattray and Hull, 2007). Other factors such as age, gender, trauma or other medical diagnosis and LOS have

been identified as parameters that may affect the QOL outcome and results in the delay of the recovery process (Dowdy et al., 2005; Davydow et al., 2008; Feng et al., 2009).

The ability to tend to bodily functions and the dependency or reliance on others was still reportedly increased at six months after ICU stay (Hofhuis et al., 2008; Kelly and McKinley, 2010; Stricker et al., 2011). In a study done where a literature review on the topic of QOL was conducted, it was found that a majority of studies did not establish the pre-admission or baseline QOL (Dowdy et al., 2005; Stricker et al., 2011). However, studies that measured patients' pre-admission QOL found that QOL of patients who had undergone prolonged MV or ICU stay remained decreased after discharge from ICU (Dowdy et al., 2005). A study conducted by Hofhuis et al. (2008) and Stricker et al. (2011) identified the absence of studies that followed up on patients long enough to assess the resultant effects of critical illness. In a study that followed up on patients nine years following discharge from ICU, the results indicated that a significant amount of participants still reported a decline in their QOL, therefore confirming that they had not regained their pre-admission QOL status (Dowdy et al., 2005; Stricker et al., 2011). Furthermore, Albeha et al. (2007) reported that six months after discharge from ICU, 34% of the patients were still dependant on caregivers for at least one personal ADL such as bathing, dressing, transfers, feeding and continence as measured by the KATZ ADL scale. Sixty percent were still reliant in the instrumental ADL functions such as use of public transport and shopping for food (Albeha et al., 2007). Kelly and McKinley (2010) reiterate that after one to six months, dependency on others, sleep interference and reduced physical function due to weakness and breathlessness that limited mobility was of a concern to most patients.

Chang et al. (2005) studied the effects of using the IMT after extubation and chronic critical illness. The result of their study suggests that if patients were exposed to a controlled rehabilitation programme the functional limitations would have been improved. Chang et al. (2005) further reported that after the Threshold® IMT training, the patients were independent in all functions as measured by the KATZ ADL scale in four to six days after ICU discharge and the 6MWT had improved significantly.

2.8 CONCLUSION

There is a need to understand the effects of intubation and MV on lung tissue, especially with regards to the inevitable inflammatory responses. The effect of this

process reportedly leads to prolonged MV and ICU LOS. The state of bed rest, coupled with catabolism and insufficient anabolic process result in further deterioration of the musculoskeletal system. There is marked muscle weakness during critical illness and this further leads to prolonged MV and LOS. Inspiratory muscle weakness has been reported to lead to failure to wean from MV and may result in extubation failure. Some studies have suggested that IMT be introduced in the beginning stages of MV so as to curb the effects of muscle weakness. The evidence available to support the use of IMT in MV patients is inconsistent; this is due to the different training methods that are adopted by different researchers. The role of physiotherapy in critical care is well studied; however its role in increasing diaphragmatic strength and contributing to decreasing re-intubation rate after extubation has not been explored.

Critical illness has an impact on the ability to carry out ADL's. This in turn affects the QOL of those recovering from critical illness as once independent people are subjected to becoming dependent on others for the most basic activities. If the exercise tolerance is reduced by the prolonged period of bed rest or the increased perception of SOB, this further hinders patients' capability to carry out ADL as they recover from critical illness. Chapter 3 describes the methodology followed to investigate these factors in a South African critical care population.

CHAPTER 3

3. METHODS

The methodology discussed in this chapter is based on the findings of the literature review discussed in Chapter 2. The study design, sample population, inclusion and exclusion criteria as well as instrumentation and data collection procedure used during the study are discussed in detail. An explanation of the pilot study, its aims, methodology and its implications on the main study procedure is given. The methods for data analysis are given as well as the ethical considerations that were taken into account when the study was conducted.

3.1 STUDY DESIGN

A single-blinded RCT was performed to ascertain the factuality of this study. The RCT was conducted over the January 2013 to August 2014 period. The randomisation technique used applied this formula `=IF(RAND()>1/2,"Group 1","Group 2")` in Excel to generate the randomisation list. The researcher identified and enrolled participants who met the requirements for inclusion in the study. The research assistant was responsible for allocating the participants into the control and intervention group.

3.2 SUBJECTS

3.2.1 Study Site and Sample Selection

The RCT was conducted at a quaternary academic hospital in Johannesburg. The study population consisted of patients with critical illness who were admitted to the general and surgical ICU. Consecutive sampling was used to identify the study sample.

3.2.1.1 Inclusion criteria

Patients were included in this trial if they were 18 years or older, male or female, admitted into the general or surgical ICU, extubated after a duration of MV of 24 hours or longer and had an intact chest wall.

3.2.1.2 Exclusion criteria

The following patients were excluded from the study:

- Unable to follow commands
- Pregnancy

- Unable to mobilise after extubation due to amputation or complex fractures of the lower limbs
- Pre-existing chronic respiratory disease
- Burns to the thorax
- Critical illness polyneuropathy/myopathy
- Thoracic surgery
- Pre-existing congestive cardiac failure /cardiac diseases
- Oncology
- Neurological diseases that influenced the patient's ability to mobilise (spinal cord lesion/Guillain Barre syndrome/ cerebrovascular accident/ myasthenia gravis).

3.2.2 Hypothesis

Null hypothesis – There is no difference in patient re-intubation rate after extubation following critical illness and prolonged MV, when IMT is added to standard in-hospital physiotherapy rehabilitation.

Alternative hypothesis – The addition of IMT to standard in-hospital physiotherapy rehabilitation of patients after extubation, following critical illness and prolonged MV, leads to a lower re-intubation rate than standard in-hospital physiotherapy rehabilitation alone.

3.2.3 Sample Size

The primary outcome of this study was incidence re-intubation, measured as re-intubation rate for ease of reference. This was determined by the strength of the inspiratory muscles measured as maximal inspiratory pressure (PiMax). Mean improvement in PiMax of 8 cmH₂O has been reported in the ICU population following IMT (Moodie et al., 2011). In the absence of established minimum clinically important difference in PiMax for the ICU population, it was decided to use 8 cmH₂O. Yang et al (1993) reported the best estimate of standard deviation for PiMax in an intubated population as being 4.5 cmH₂O. A total of 7 subjects would provide an 80% probability of detecting a difference of 8 cmH₂O in PiMax with alpha of 5%. To account for non-compliance with treatment and death in the critically ill population, the sample size was increased to 14 subjects per group.

3.2.4 Variables

Dependent variables:

The dependent variables for the RCT were:

- PiMax and PeMax
- Rate of re-intubation
- SOB
- Six minute walking distance test (6MWT)
- ADL
- QOL

Independent variable:

The independent variable was the administration of IMT after extubation.

Confounding variables:

The confounding variable was the patients' HIV status.

3.3 ETHICAL CONSIDERATIONS

Ethical clearance was obtained from the University of the Witwatersrand (M120473) to perform this study (Appendix 1). Permission was also obtained from the Head of Clinical Services of the quaternary hospital in Johannesburg to perform the study (Appendix 2). The study was registered with the South African National Clinical Trials registry (DOH-27-0614-4750) (Appendix 3). Admission into an ICU for a scheduled or unscheduled medical procedure is a traumatic experience and there is an increased probability that patients may develop post-traumatic stress disorder (PTSD) or anxiety after surviving the ordeal (Davydow et al., 2008). Therefore the inclusion of a temporary consent was considered for this study. Temporary consent (Appendix 4) for inclusion of patients who were eligible for the study was obtained from the ICU manager, consultant or the patient's family for the period that the patient was still in the ICU. An information sheet (Appendix 5) was made available to suitable patients. Patients were advised about the purpose of the study, a brief explanation of what was required of them and that they were free to withdraw from the study at any time without penalty to them and without their standard medical or physiotherapy care being compromised as a result of their decision. Informed written consent (Appendix 6) was obtained from those patients who were willing to participate in the study, in the presence of the ward sister on duty or the unit manager. The patients' demographic information (Appendix 7) forms were coded to ensure that the participant details remained anonymous.

3.4 STUDY PROCEDURES

3.4.1 Instrumentation

- Inspiratory muscle training (IMT) was administered through the Threshold® IMT device: Respiration HS730EU (Figure 3.1).



Figure 3.1: Threshold® IMT Device

- Maximal inspiratory and expiratory pressure: PiMax and PeMax was measured through a tight fitting face mask which was attached to a pressure manometer via tubing (Figure 3.2) to measure negative inspiratory force (NIF) and positive expiratory force (PEF).

PiMax and PeMax measurements have been reported to assess the decreased inspiratory muscle strength in intubated and spontaneously breathing patient populations (Gayan-Ramirez et al., 2002; Chang et al., 2005). The instrument has also been used to report on the improvement after IMT training in chronically critically ill patients (Chang et al., 2005; McConnell, 2013). For this study the NIF and PEF tubes were made from clear tubing 7mm x 30mm; a length of 30-40 cm was connected to the manometer using a Smiths Medical International 15mm adaptor FHO52-A 387 (Evans and Whitelaw, 2009). This tube served as a connection between the manometer and the face mask.

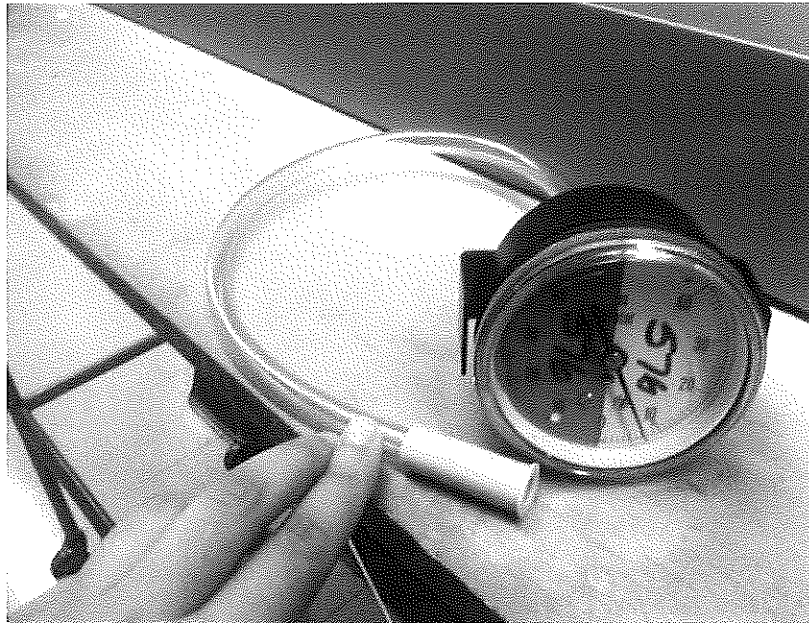


Figure 3.2: Manometer and NIF/PEF Tube

- Shortness of breath (SOB) was measured using the Modified BORG scale (0-10) (Appendix 9). Chang et al. (2005) utilized the BORG scale as an indicator of perceived fatigue in a study conducted in chronic critically ill patients that underwent an IMT training programme. Amedei (2012) and Elliot et al. (2011) stated that the Modified BORG scale has been shown to be a standardized tool, which assists in gauging exercise intensity and identifying safety measures that need to be considered when treating patients in a critical care setting.

- Cardiovascular endurance was measured with the six minute walk test (6MWT). The test was performed in the respective wards. This was done so that there would be other professionals around to assist the researcher in case of an emergency and to accommodate patients on oxygen especially in instances where portable oxygen tanks were not available. A tape measure was used to measure a distance of 12 metres and two cones were placed to mark the end points. A chair was made available and placed midway and along the corridor to avoid obstructing the corridor and hindering the activities in the ward. The wards where the tests were performed were not conducive to applying the recommended 30 meter distance as stipulated by the American Thoracic Society. The ward corridors were often occupied by other patients, nurses or professionals attending general ward rounds that would disrupt the patient's pace and concentration. Thus the distance was decreased to control the external environmental factors that would deter the patient's performance. A clip board was used to record heart

rate (HR), blood pressure (BP) and respiratory rate (RR) on a data capturing sheet. A cell phone timer was used to monitor the time it took each participant to complete the 6MWT.

- Peripheral capillary oxygen saturation (SpO₂), BP and HR were measured by the use of a monitor: Biocare, model BM-9000S or DINAMAP model DPC321N-EN. Elliot et al. (2011) reported that the 6MWT was an adequate tool to use to measure exercise capacity in the different stages of recovery from critical illness.
- Quality of life (QOL) was measured using the EQ-5D questionnaire (Appendix 10). A systematic review that evaluated the QOL of patients after critical illness, considered the EQ-5D to be a valid and reliable instrument to use in critically ill patients (Oeyen et al., 2010).
- Activities of daily living (ADL) were measured with The Health Assessment Questionnaire (HAQ) (Stanford University School of Medicine) (Appendix 8). This tool has been used for assessment of many patients with conditions other than rheumatoid arthritis (Toussiot, 2010). Bruce and Fries (2003) further state that the HAQ is a reliable measurement instrument and that the face and content validity and the construct validity have been proven in numerous clinical trials.
- Simplified Acute Physiology Score II (SAPS II), (Appendix 11) was used to predict the severity of illness in a critical care setting and thus predict mortality (Prakash et al., 2006). It measures 12 physiological variables and three variables related to the diagnostic reason for admission to ICU (Prakash et al., 2006). It was concluded that patients with a SAPS II score of 51-60 points (62.5%) had a high mortality rate and a decreased rate of survival. A significant association has been reported between the scores and the number of patient deaths (Prakash et al., 2006).
- Acute Physiology and Chronic Health Evaluation II (APACHE II) (Appendix 12). Prognostic assessments are vital in a critical setting, APACHE II has been reported to evaluate the severity of illness and accurately stratify the mortality rate (Naved et al., 2011).
- Body weight measuring scale: Beurer mechanical bathroom scale (MS01).

- Height measure: The Leicester height measure, distributed by child growth foundation. Manufactured by TA plastics LTD.

3.4.2 Data Collection Procedure

During the course of this RCT, the researcher was responsible for assessing the outcome measures at various time points during the trial. The research assistants were responsible for administering daily treatment interventions (determined by group allocation) to trial participants.

3.4.2.1 Before the pilot study

The researcher conducted in-service training with the research assistants who would be performing the interventions during the RCT. The use of the IMT device was explained and demonstrated. The researcher was used as a mock patient for the research assistants to practice the administration of IMT and the instructions that would be given to the patients. The researcher and the research assistants concluded that it was a simple and easy tool to administer. No problems were foreseen with regards to patients understanding the instructions in spite of the diverse languages we are exposed to in the hospital. Questions and concerns that the research assistants had with regards to progression of treatment were addressed during this training session. The research assistants were given a file that comprised of the printed copy of the Excel randomization list, patient progress notes (Appendix 13), the IMT (Appendix 14) and physiotherapy (Appendix 15) standardized treatment sheet.

3.4.2.2 Pilot study

The aim of the pilot study was to assess the feasibility of the study, to evaluate the period it would take to acquire consent (temporary and informed consent) and to perform the baseline measurements. The researcher's task was to perform the baseline measurements and evaluations of PiMax, PeMax, BP, HR, SpO₂, and Modified BORG scale rating, HAQ and EQ-5D at the point of extubation. These measurements were repeated at discharge from hospital and at one and three months after discharge. The 6MWT was introduced and assessed at hospital discharge respectively, one and three months after discharge. Once the baseline assessment by the researcher was completed the research assistant consulted the randomization list and allocated a participant number to the patient and commenced with the appropriate treatment.

The initial challenge was getting the staff members (some doctors in the trauma unit, the sister in charge of the unit and the shift sisters in some ICU) to sign the temporary consent on behalf of the patients. Although aware of the study, it is believed that some staff members did not understand that they acted purely as witnesses and proxy, and that each patient still had the right to withdraw from the study after discharge from ICU when requested to sign the informed consent. A meeting was held with the heads of the unit and the matter was resolved and clarified. It proved difficult to attain interest from most patients on the day they were extubated. The response was mainly 'give me time' or 'come back tomorrow.' The decision made was that suitable patients would be approached one day after they were extubated. The patients were not comfortable signing consent or having someone sign consent on their behalf. Some patients gave verbal consent and opted to give their written consent they are discharged to the ward or 'felt better.'

The pilot study consisted of four patients who were selected based on the inclusion criteria.

The assessment of BP, HR, SpO₂ and PiMax and PeMax required approximately 10 to 15 minutes to perform. Most of the patients could not read English and therefore the Zulu version of the EQ-5D was made available. However, it was noted that although patients understood spoken Zulu, most were unable to respond to the written format of the language. Although translations and translators were sought, most patients responded better to interview based questions. Ultimately the researcher conducted interviews, instead of using a self-administered method, to assist the participants in the completion of all questionnaires. The Stanford HAQ questionnaire (Appendix 8) was used to assess ADL. For the relevance of this study only the disability index section was completed. The Modified BORG scale (Appendix 9) and EQ-5D questionnaire (Appendix 10) were completed in approximately 15-20 minutes. The BORG and EQ-5D were quicker and seemed easier for the patients to complete than the HAQ questionnaire. The HAQ proved to be more complex to complete, this was due to the additional option made available, namely 'with much difficulty' which confused patients. The research assistant conducted the pilot intervention programme as outlined in Appendix 14 and 15. The researcher attended two treatment interventions which included the IMT to assess whether the research assistant was using it correctly and optimally. Thereafter the research assistant consulted with the researcher when needed. The 6MWT was introduced and measured when the patient was being discharged from the hospital. Vital signs were

measured and recorded as per 6MWT protocol and the PiMax and PeMax were also re-evaluated at this stage. Questionnaires were completed at discharge and only the Modified BORG scale was repeated after the 6MWT assessment was completed. The preparation and the performance of the 6MWT took approximately 10 minutes. This process was repeated at the follow-up appointments at one and three months after discharge respectively.

The outcome measurements proved to be too much for one session for most of the patients, thus HR, RR, BP, SpO₂, PiMax and PeMax, HAQ, Modified BORG scale and EQ-5D questionnaires were assessed in the first session and the weight and height were assessed in the second session, which was usually the next day. Therefore, some patients did not cope if treatment was administered on the same day as the first session baseline measurements. The decision was made to commence treatment the day after the first session of baseline measurements were completed. Communication between health professionals with regards to discharge plans was not always documented or patients were not always adequately informed. This resulted in some patients being missed at discharge or transferred to other institutions prior to the researcher repeating the outcome measurement assessments. Strategies to improve communication with the ward team were put in place by the research assistant and researcher to overcome this problem and therefore to avoid missing more patients at discharge or transfer. The researcher decided that patients who opted not to consent for the study after two treatments from the research assistant on the ward be removed from the trial and handed over to the relevant physiotherapist assigned to that ward who continued with standard treatment. The study procedure was divided into four phases. Phase one (on the day of extubation) entailed signing of the information document and temporary consent and the researcher the calculation of the SAPS II (Appendix 11) and APACHE II (Appendix 12) scores. During this period the research assistant allocated the patients into either the control and intervention group. One day after extubation phase two was implemented, which included the subjective assessment, the measurements of vitals, PiMax/PeMax, the completion of the questionnaires and the commencement of physiotherapy treatment. Phase three was implemented on day three following extubation (consisted of the BMI calculations which included taking the measurements for weight and height). Phase four entailed attaining the informed consent on the ward from participants.

3.4.2.3 Main study

In the main study, after extubation, the research assistants administered the physiotherapy treatment programme as outlined in Appendix 12 and the IMT programme for the experimental group as outlined in Appendix 13. Subjects were randomly allocated to the control or intervention group using a computer-generated list that was obtained using Excel 2010 and the formula =IF (RAND ())>1/2, "Group 1", "Group 2").

The main study was a single blinded study where the researcher performed all outcome measurements and was not aware of which patients were allocated to the intervention or control groups. The randomization list was managed by the research assistants who kept it with their patients' progress notes. Patients who were intubated and ventilated for at least 24 hours were tracked until the day of extubation. During this time, patients who demised or developed secondary conditions that were part of the exclusion criteria were identified and the track list was updated accordingly. The researcher screened the ICU in the mornings (Mondays to Friday) and identified patients that were suitable for the study as outlined in the inclusion criteria. Patients that were admitted late in the afternoon or evening of the previous day were screened early the next morning. Routine ICU physiotherapy treatment entailed chest physiotherapy techniques, suctioning, peripheral limb exercises and mobilization. These were administered once a day and if required a second treatment was administered.

Phase 1

When the patients were extubated, the researcher informed the patients about the study. The Sister-in-Charge or Unit Manager in the ICU was asked to bear witness when the patients read the information sheet or the researcher read the information sheet to the patient. If the patient agreed to take part in the study they were asked to sign the information sheet and the Sister-in-Charge or Unit Manager signed the temporary consent on behalf of the patient. Some patients were discharged from the ICU without being awake and alert enough to be informed about the study, as at the time they could not follow commands. The researcher followed up on these patients in the ward. In the event that the patient was able to follow commands then the patient was informed about the study. If the patient agreed to participate they signed the information document and the temporary consent was signed by the Sister-in-charge or Unit Manager in the respective wards.

Phase 2

The researcher interviewed the patients to attain demographic information (Appendix 12) and create a rapport with the patients who were often wary of what was expected of them. In order to complete the questionnaires the researcher interviewed the participants. The participants' response was not influenced by the researcher in any way when the questionnaires were being completed. The HAQ (Appendix 9) was completed first, in the form of ticks next to the relevant answers. Afterwards patients identified their level of perceived dyspnoea on the Modified BORG scale. The scale ranged from 0 to 10 and the patient circled the number or indicated with their finger to the researcher which number they felt identified their level of dyspnoea. Thereafter the EQ-5D was completed by the use of ticks next to the relevant answer/s.

Baseline vital signs were measured as follows:

The patient was asked to sit up in the bed or chair. The bedside monitor blood pressure cuff was placed on the left upper arm and three measurements were taken. The mean was recorded as the blood pressure at the time of assessment in mmHg. Simultaneously the heart rate was measured from the patient's bedside monitor or from the SpO₂ finger probe.

Baseline PiMax and PeMax were measured as follows:

PiMax and PeMax were measured with a manometer that was connected to a silicone face mask via a negative inspiratory force (NIF) and positive expiratory force (PEF) tube.

The patient was requested to inhale and exhale maximally through the face mask and the reading was measured by the manometer. The best of three measurements was recorded.

The initial training resistance for IMT device was then calculated by using 30% of the measured PiMax value. The researcher made this value available to the research assistant for all participants before treatment was commenced. The researcher noted the value and the initial intensity on the progress notes forms (Appendix 13). Prior to commencing with the intervention aspect of the study, the research assistant randomly assigned participants into the control or intervention group through the use of the computer generated randomization list as previously explained. Thereafter, the

research assistant assigned a participant number and commenced with treatment. Patients were given one physiotherapy treatment and/or IMT session per day from Monday to Friday, until the day of hospital discharge. However, if indicated a second physiotherapy session without the IMT intervention would be administered.

Phase one and two did not always occur on different days. If the patient was extubated in the morning both phases would occur on the same day and the patient would be treated on day one after extubation. In some cases where the patient was extubated in the afternoon, phase one would occur that same afternoon or the next morning. The treatment interventions would then occur at the very least day two after extubation.

Phase 3

The main aim of this phase was to calculate the participant's weight and height. Increased BMI (body mass index) could result in decreased exercise tolerance (Iida et al., 2010). It was decided that the patients' BMI be assessed to assist with analysis of 6MWT findings. The patients' weight was assessed by using the Beurer mechanical bathroom scale. The Leicester height measure was used to measure the height. The height and weight were used to calculate the BMI by using the BMI metric formula, $BMI = (\text{Weight in kilograms} / (\text{Height in meters})^2)$. If the patient was unable to stand for the duration of the measurements, an estimate of the weight and height was noted as advised by the dietician.

Phase 4

The patient was requested to sign the informed consent form if they wished to continue with the study. Patients who chose to withdraw were referred to the ward Physiotherapist.

3.4.2.3.1 Physiotherapy management for control group subjects

Treatment for control group subjects commenced during the phase two period.

The standard physiotherapy treatment based on recommendations made by Gosselink et al. (2008) was administered to the control group by the research assistant (Appendix 14).

For aerobic training and muscle strengthening the initial time period was 5 minutes and was progressed according to each patient's ability. Progression was graded by increasing the weight of the object used for strength training and increasing the repetitions.

Mobilization was graded according to what the patient was able to manage and was documented by the research assistant. Physiotherapy treatment was administered to patients until the day they were discharged from the hospital.

3.4.2.3.2 Physiotherapy management for intervention group subjects

Treatment commenced during the phase two period for the intervention group.

The research assistant performed the same treatment guidelines as stated above for the control group. However, the intervention group also performed IMT with the Threshold® IMT device. The initial training began at 30% of each individual subject's PiMax as stated above. The research assistant educated and demonstrated the use of the IMT to the patient as described by the Respirationics User Guide (2000) (see Appendix 15). The duration of time that the patient performed the IMT was gradually increased to 30 minutes. When the patient managed to perform IMT for 30 minutes, the intensity was increased by 10% of baseline PiMax until 50% of baseline PiMax was reached as this was the predetermined maximal training intensity for this study. The IMT and physiotherapy treatment were continued until the patient was discharged from the hospital.

3.4.2.3.3 Patient assessment at hospital discharge

Outcome measures (PiMax/PeMax, HAQ, Modified BORG scale, EQ-5D questionnaires), performed at extubation were re-assessed. Vitals (HR, RR, BP, SpO₂) were performed before the patient performed the 6MWT. Cardiovascular endurance was measured at discharge using the 6MWT. The patient was informed that they would walk for six minutes at a pace that was comfortable for them. They were advised to inform the researcher if they felt dizzy or faint and if they needed to take a break. When the patient was ready, the researcher set the timer for six minutes and the patient commenced with the test. The researcher observed the patient and counted the number of laps performed and monitored the patient for untoward symptoms. Throughout the

test, verbal prompts were given to encourage the patient to complete the test and make them aware that they were doing well. Once the six minutes had lapsed, the patient was given two minutes to recover and the vitals outcome measurements were performed again. The Modified BORG scale was used to determine the patient's level of perceived dyspnoea after the test, which was then documented on the outcome measurement sheet.

The researcher made provisional appointments for the patients. The research and appointment detail document was given to the patients. Appointments were confirmed telephonically. Patients were given the researcher's number to improve and encourage communication throughout the follow-up process. A reminder phone call was made to all patients two weeks and one day before the scheduled appointment date respectively.

3.4.2.3.4 **One and three months after discharge**

The researcher obtained verbal permission from the orthopaedic trauma or COPD clinics to use some of the clinic space for all follow-up assessments and all attempts were made to use similar instrumentation to those used during the patients' hospital stay to evaluate vital signs. At one and three months follow-up appointments all the outcome measures (PiMax/PeMax, HAQ, Modified BORG scale, EQ-5D questionnaires) were performed. The corridor length at the clinic allowed for an increase in the 6MWT distance to 25 meters (measured with a measuring tape) from the 12 meters used in the hospital wards. At the completion of the 6MWT the Modified Borg scale was re-evaluated. After each of the follow-up sessions each patient was reimbursed for their transport cost as outlined in the information document.

3.5 **STATISTICAL ANALYSIS**

Data was captured and entered on an Excel spreadsheet. The IBM Statistical Package for Social Sciences (SPSS) version 21 for Windows was utilized to analyse data collected.

Categorical data such as gender were summarised as numbers and percentages. Continuous data were summarized using means and standard deviations (SD). Intention-to-treat and per-protocol analysis was used to determine the effect of IMT training on patient outcome. In the Intention-to-treat analysis (ITT) data from all participants was included for analysis in the groups to which they were originally

randomised. For missing data, the principle of 'last value carried forward' was applied (Shah, 2011). The only data that was not carried forward was that of participants who had demised at certain time points in the study. Per Protocol analysis (PP) compared data between the intervention and control groups but only for participants who completed the treatment to which they were originally allocated (Shah, 2011). This analysis evaluated only data that was available at all the different time points. Groups were compared with respect to categorical parameters using the Chi-square test and the Fischer's exact test. On the day of hospital discharge and at one and three months after discharge respectively, one-way analysis of variance (ANOVA) was used to assess changes in outcomes within each group at these time points. For changes in outcome measures over time, the control and intervention groups were compared using repeated measures analysis of co-variance (ANCOVA). Testing was done throughout at the 0.05 level of significance.

CHAPTER 4

4. RESULTS

This chapter describes the results obtained from the RCT as described in the previous chapter. Statistical analysis tests were used to attain these results.

A total number of 2,300 patients were admitted into the ICU of the quaternary hospital in the period between June 2012 and June 2014. Of the 2,300 patients, 2,145 were excluded and 155 patients were identified as being suitable for the study. Figure 4.1 illustrates the flow of patients through this study. A total of 30 patients consented to participating in the study of which 14 patients were allocated to the control group and 16 patients were allocated to the intervention group (Figure 4.1).

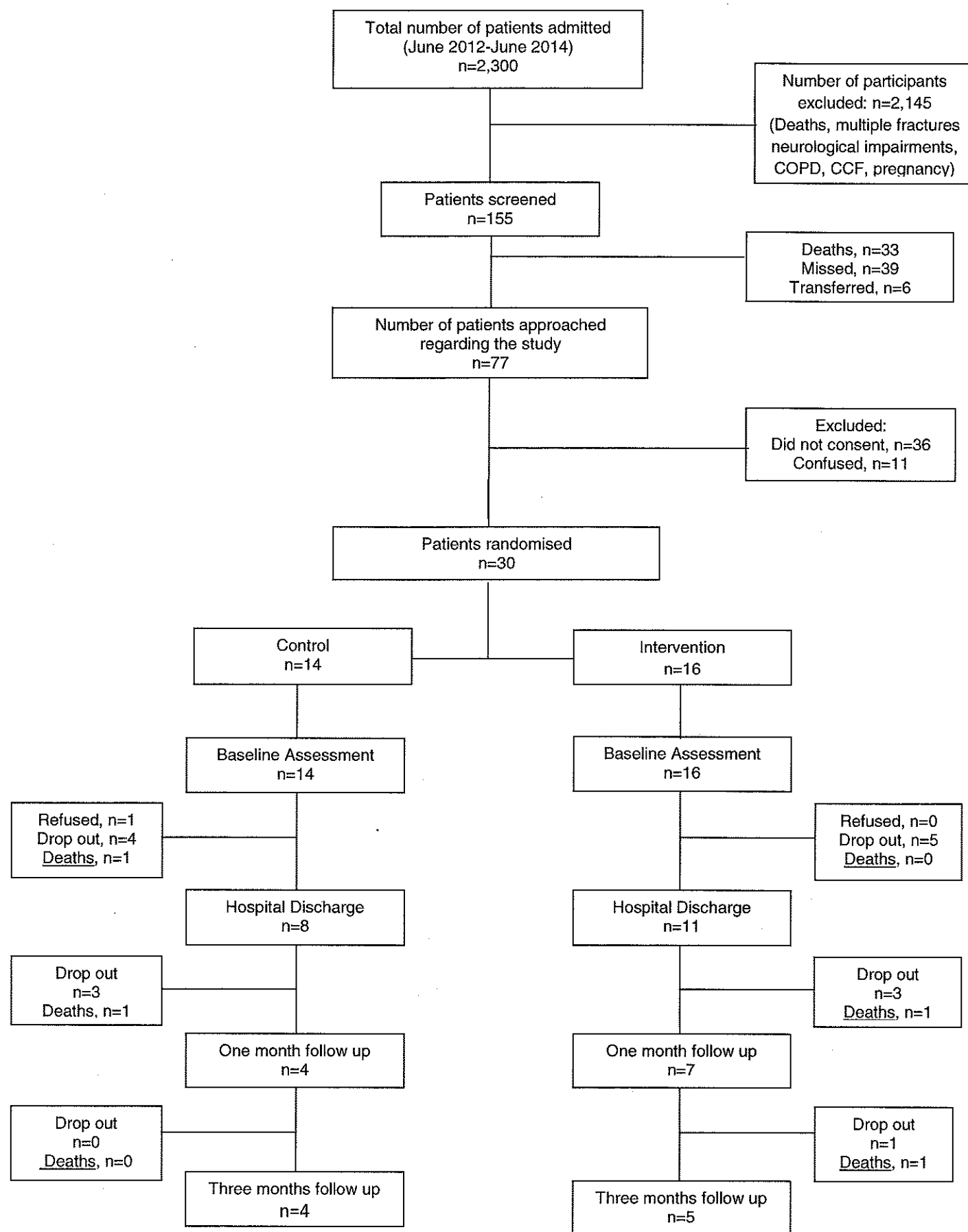


Figure 4.1: Flowchart of Patient Participation in the Study

4.1 DEMOGRAPHICS OF THE STUDY POPULATION

Figure 4.2 provides a visual representation of the gender distribution of participants in the trial.

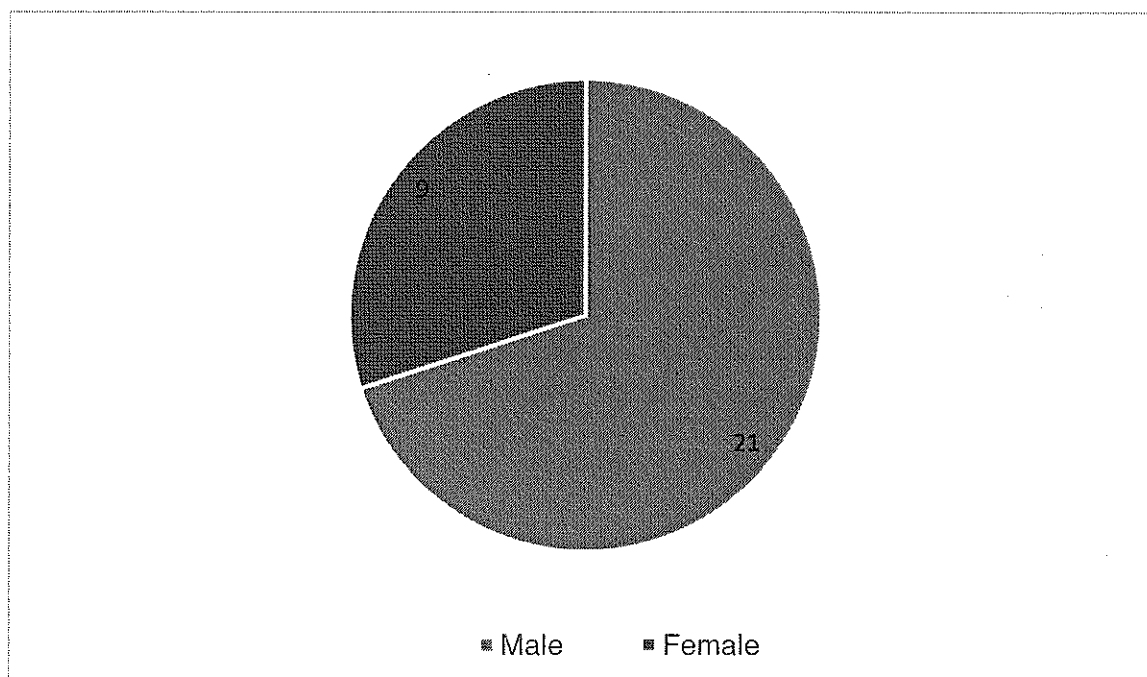


Figure 4.2: Gender Distribution of Study Participants (n=30)

The study participants were mainly male 70% (n=21) and 30% (9) were female. In the control group the males accounted for 71.4% (n=10) and females for 28.6% (n=4) of the participant group, and the intervention group had 52.4% (n=11) males and 55.5% (n=5) females. No statistical difference ($p=0.87$) was observed within the two groups in relation to gender.

Table 4.1 expresses the descriptive variables of the two participating groups. The total of both groups and the p-value have also been tabulated for ease of reference.

Table 4.1: Descriptive Information of Participants

Demographic Variables	Control Group (n=14)	Intervention Group (n=16)	Total (n=30)	p-value
Age (years)	39.3 (± 15.3)	34.7 (± 9.8)	36.9 (± 12.6)	0.05
Duration of MV (days)	4.7 (± 6.1)	7.6 (± 10.3)	6.2 (± 8.6)	0.42
ICU LOS (days)	5.2 (± 5.2)	9.3 (± 11)	7.4 (± 8.9)	0.16
Hospital LOS (days)	10 (± 8.6)	38 (± 37.7)	25.2 (31.2)	0.01
APACHE II	27.4 (± 25.9)	15.5 (± 11.1)	21 (± 20.1)	0.04
SAPS II	11.2 (± 13.9)	8.5 (± 7.6)	9.8 (± 10.9)	0.07
Weight (kg)	61.3 (± 19.4)	64 (± 11.9)	62.7 (± 15.6)	0.67
Height (m)	156.1 (± 45.4)	166.1 (± 7.6)	161.4 (± 31.3)	0.08
BMI (kg/m ²)	21.8 (± 6.8)	23.1 (± 4)	22.5 (± 5.4)	0.61

*Values expressed as mean ($\pm$ SD). MV - mechanical ventilation; ICU - intensive care unit; LOS - length of stay; APACHE II - acute physiology chronic health evaluation; SAPS II - simplified acute physiology scale; BMI - body mass index.

The difference in age between the two groups was statistically different ($p=0.05$), the control group was 4.6 years older than the intervention group. A statistical significance in the LOS in hospital was observed between the two groups ($p=0.01$). The participants in the intervention group reportedly had a hospital stay of 38 days (± 37.7), which was noted as 28 days more than the 10 days (± 8.6) stay in the control group. The APACHE II and SAPS II scores were used to measure the severity of illness and predicted mortality rate of patients admitted into the ICU. The APACHE II score difference between the groups was statistically significant ($p=0.04$). The control group had a higher risk of mortality score of 27.4 points (± 25.9) as compared to the intervention group that had a score of 15.5 points (± 11.1). No statistical significance was observed within the control and intervention groups when the duration on MV, LOS in ICU, SAPS II, weight, height and BMI variables were evaluated.

Figure 4.3 demonstrates the distribution of the diagnosis categories that presented in the study population.

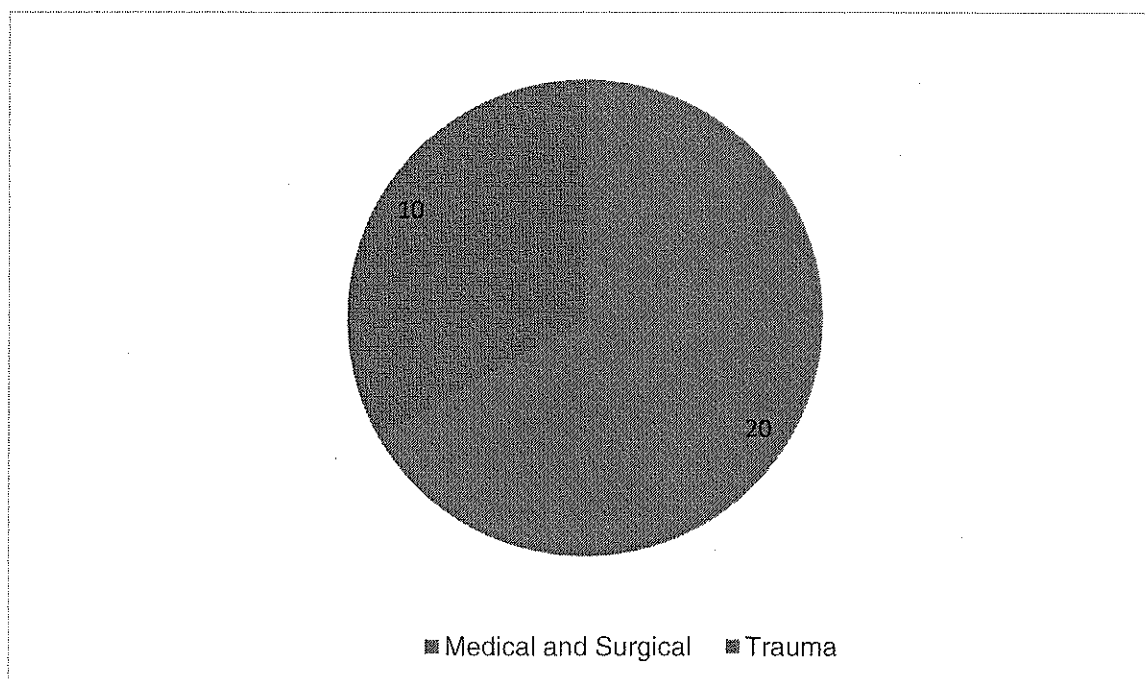


Figure 4.3: Admission Diagnosis Categories of Study Participants (n=30)

The individual admission diagnoses of subjects were categorised as either trauma-related or medical and surgical-related cases for ease of data interpretation. In the control group 28.6% (n=4) of the participants had a trauma-related diagnosis and 71.4% (n=10) had a medical or surgical diagnosis. Trauma-related conditions accounted for 37.5% (n=6) of the participants in the intervention group and 62.5% (n=10) of the participants in the intervention group had a medical and surgical condition. No statistical difference ($p=0.60$) was noted within the groups with regards to diagnosis.

Table 4.2 demonstrates the difference in baseline vitals measurements at extubation.

Table 4.2: Difference in Vital signs between Groups after extubation

<u>Vitals</u>	<u>Control Group</u> <u>(n=14)</u>	<u>Intervention</u> <u>Group (n=16)</u>	<u>Total (n=30)</u>	<u>p-value</u>
<u>HR (bpm)</u>	<u>95.7 ($\pm$18.3)</u>	<u>101.1 ($\pm$15.5)</u>	<u>98.6 ($\pm$16.7)</u>	<u>0.39</u>
<u>SPO₂ (%)</u>	<u>97.1 ($\pm$18.3)</u>	<u>96.1 ($\pm$3.3)</u>	<u>96.6 ($\pm$3)</u>	<u>0.36</u>
<u>BP-systolic (mmHg)</u>	<u>132 ($\pm$19.4)</u>	<u>131.2 ($\pm$17.1)</u>	<u>131.6 ($\pm$17.9)</u>	<u>0.90</u>
<u>BP- diastolic (mmHg)</u>	<u>80.1 ($\pm$9.1)</u>	<u>75.2 ($\pm$12.2)</u>	<u>77.5 ($\pm$11)</u>	<u>0.23</u>

*Values expressed as mean ($\pm$ SD). HR-heart rate; bpm- beats per minute; SPO₂, Peripheral Saturation of Oxygen; BP- blood pressure.

The heart rate was slightly elevated (5.4 bpm) for the intervention group at extubation. The diastolic value was increased for the control group (80.1) when compared to the intervention group (75.2). Even though some differences were noted between the two groups, there was no statistically significance noted when the variables were compared.

The confounding variable for this study was identified as HIV status. Table 4.3 demonstrates the number of participants in the different status categories.

Table 4.3: HIV Status of Participants

	HIV Negative	HIV Positive
Control group (n=14)	71.4% (10)	25.5% (4)
Intervention group (n=16)	68.8% (11)	31.2% (5)

*Values expressed as percentages and numbers. HIV - human immunodeficiency virus.

The number of participants diagnosed with HIV was higher in the intervention group than in the control group. A statistically significant difference in HIV status was observed between the groups ($p=0.02$). Patients who were admitted due to pulmonary TB, PJP or meningitis were routinely tested for HIV in the medical ICU. In the surgical ICU patients HIV status was only tested if their pathology results, especially the white cell count (WCC), was not improving after successful surgical

intervention and haemodynamic stabilisation. The patients who did not manifest any retroviral disease symptoms were assumed to be HIV negative.

4.2 THE EFFECT OF INSPIRATORY MUSCLE TRAINING (IMT) ON RE-INTUBATION RATE AND INSPIRATORY AND EXPIRATORY MUSCLE STRENGTH

4.2.1 Re-Intubation Rate

The Chi-squared statistical test was performed to evaluate the rate of re-intubation and the difference between the control and intervention groups. Table 4.3 provides the results of the difference in re-intubation rate.

Table 4.4: Difference in Re-Intubation Rate between Groups

	Re-Intubation (n)	Not Re-Intubated (n)
Control Group (n=14)	0 (0%)	14 (100%)
Intervention Group (n=16)	1 (6.3%)	15 (93.7%)
Total (n=30)	1 (3.3%)	29 (96.7%)

*Values expressed as numbers (percentages).

The one participant that required re-intubation was in the intervention group and received both the IMT and in-hospital physiotherapy treatment. Nevertheless, the rate of re-intubation was not statistically significant ($p=0.90$) between the groups. The participant required re-intubation due to respiratory failure. She had a diagnosis of aplastic anaemia and at the one month follow-up assessment it was found that her condition had deteriorated significantly.

4.2.2 Inspiratory Muscle Strength (PiMax)

The ANOVA was performed to evaluate the difference in mean PiMax in the two groups at specified time points. Table 4.4 provides a summary of the results for both ITT and per-protocol analyses.

Table 4.5: Inspiratory Muscle Strength (PiMax) Measured within the Participant Groups at Specified Time Points

Time point for PiMax assessment	ITT			PP		
	Control (n=14)	Intervention (n=16)	p Value	Control (n=3)	Intervention (n=3)	p Value
	Mean ($\pm$ SD) (cmH ₂ O)	Mean ($\pm$ SD) (cmH ₂ O)		Mean ($\pm$ SD) (cmH ₂ O)	Mean ($\pm$ SD) (cmH ₂ O)	
Extubation	82.3 ($\pm$ 25.7)	93.2 ($\pm$ 13.1)	0.14	94 ($\pm$ 18.2)	85 ($\pm$ 0)	0.44
Discharge	79.2 ($\pm$ 36.7)	95.4 ($\pm$ 14)	0.11	104.3 ($\pm$ 31)	91.6 ($\pm$ 2.8)	0.52
1- month	72.7 ($\pm$ 42.1)	93.7 ($\pm$ 14)	0.71	102.6 ($\pm$ 32.3)	86 ($\pm$ 1.7)	0.42
3- months	73.2 ($\pm$ 41.5)	90.8 ($\pm$ 29.4)	0.18	105 ($\pm$ 21.7)	90 ($\pm$ 16.3)	0.31

*Values expressed as mean ($\pm$ SD). PiMax - maximal inspiratory mouth pressures; ITT - intention to treat; PP - per protocol.

With ITT analysis there was a 9.1cmH₂O reduction in mean PiMax from the time of extubation to the three month follow- up for participants in the control group. In the intervention group there was a smaller reduction (2.4cmH₂O) in mean PiMax over the same time period. However with per protocol analysis this was not the case. There were no statistically significant differences in PiMax between the groups at the different time points using either one of the analyses.

To determine if the intervention had an effect on PiMax over time, the groups were compared using ANCOVA. For ITT analysis, there was no statistically significant differences between the groups over time ($p=0.11$). The same result was found with per protocol analysis ($p=0.16$).

4.2.3 Expiratory Muscle Strength (PeMax)

The ANOVA was performed to evaluate the difference in mean PeMax in the two groups at specified time points. Table 4.5 provides a summary for both ITT and per-protocol analyses.

Table 4.6: Expiratory Muscle Strength (PeMax) Measured within the Participant Groups at Specified Time Points

Time points for PeMax assessment	ITT			PP		
	Control (n=14)	Intervention (n=16)	p Value	Control (n=3)	Intervention (n=3)	p Value
	Mean ($\pm$ SD) (cmH ₂ O)	Mean ($\pm$ SD) (cmH ₂ O)		Mean ($\pm$ SD) (cmH ₂ O)	Mean ($\pm$ SD) (cmH ₂ O)	
Extubation	75.7 ($\pm$ 40.4)	79.8 ($\pm$ 15.5)	0.71	108.3 ($\pm$ 32)	75 ($\pm$ 18)	0.16
Discharge	71.5 ($\pm$ 41.1)	98.8 ($\pm$ 21.7)	0.02	93.3 ($\pm$ 7.6)	130 ($\pm$ 21.7)	0.05
1- month	66.7 ($\pm$ 41.8)	88 ($\pm$ 22.7)	0.08	88.3 ($\pm$ 20.8)	93.3 ($\pm$ 5.7)	0.70
3- months	81.7 ($\pm$ 49.4)	89.8 ($\pm$ 28)	0.58	135 ($\pm$ 5)	108.3 ($\pm$ 10.4)	0.01

*Values expressed as mean ($\pm$ SD); PeMax - maximal expiratory mouth pressures; ITT - intention to treat; PP - per protocol.

With ITT analysis, there was a gradual increase in expiratory muscle strength from extubation to three months after discharge for participants in both the control and intervention groups. With per protocol analysis a similar trend is seen over the same time period for participants in both groups. At discharge from hospital the intervention group had a significantly higher PeMax than the control group for both the ITT analysis ($p=0.02$) and per protocol analysis ($p=0.05$). However, at three months following discharge the control group had a significantly higher PeMax ($135\pm5\text{cmH}_2\text{O}$) compared to the intervention group ($108.3\pm10.4\text{ cmH}_2\text{O}$) using per protocol analysis ($p=0.01$). The ITT analysis at three months did not support this finding.

To determine if the intervention had an effect on PeMax over time, the groups were compared using ANCOVA. For ITT analysis, there was no statistically significant differences between the groups over time ($p=0.91$). The same result was found with per protocol analysis ($p=0.80$).

4.3 THE EFFECT OF INSPIRATORY MUSCLE TRAINING ON PERCEPTION OF BREATHLESSNESS

The ANOVA was performed to evaluate the difference in mean BORG ratings in the two groups at specified time points. Table 4.6 provides a summary for both ITT and per-protocol analyses.

Table 4.7: The Comparison of the Perception of Breathlessness as Measured by the BORG Scale within the Participating Groups at the Specified Time Points

BORG Rating	ITT			PP		
	Control (n=14)	Intervention (n=16)	p Value	Control (n=3)	Intervention (n=3)	p Value
	Mean ($\pm$ SD)	Mean ($\pm$ SD)		Mean ($\pm$ SD)	Mean ($\pm$ SD)	
Extubation	1.1 ($\pm$ 2.3)	1 ($\pm$ 2.6)	0.93	4.3 ($\pm$ 3.7)	0 ($\pm$ 0)	0.11
Discharge	0.6 ($\pm$ 1.8)	0.7 ($\pm$ 1.9)	0.91	2.3 ($\pm$ 4)	0 ($\pm$ 0)	0.37
1- month	0.2 ($\pm$ 0.57)	0.5 ($\pm$ 1.9)	0.66	0.8 ($\pm$ 1)	0 ($\pm$ 0)	0.23
3- months	0.1 ($\pm$ 0.3)	0.5 ($\pm$ 1.9)	0.48	0.3 ($\pm$ 0.2)	0.1 ($\pm$ 0.2)	0.51

*Values expressed as mean ($\pm$ SD), ITT - intention to treat; PP - per protocol.

There was a gradual reduction in the level of perceived breathlessness from extubation to three months after discharge in both the control and intervention groups with the ITT analysis. Per protocol analysis showed a large reduction in the level of perceived breathlessness during the same time period for the control group. There were no statistically significant differences in level of perceived breathlessness between the groups at the specified time points using both the ITT and per protocol analyses.

Similarly when the ANCOVA was performed to compare the effects of the intervention over time, the results yielded from the ITT analysis were not statistically significant ($p=0.73$). The same was found with the per protocol analysis ($p=0.45$).

4.4 THE EFFECT OF INSPIRATORY MUSCLE TRAINING ON EXERCISE ENDURANCE AS ASSESSED WITH THE 6MWT

4.4.1 Distance (m) Walked with the 6MWT

The ANOVA was performed to evaluate the difference in the distance walked as measured by the 6MWT between the two groups at specified time points. Table 4.7 provides a summary for both ITT and per-protocol analyses.

Table 4.8: Comparison of the Mean Distances Walked within the Participating Groups at the Specified Time Points

6MWT (Distance walked)	ITT			PP		
	Control (n=14)	Intervention (n=16)	p Value	Control (n=3)	Intervention (n=33)	p Value
	Mean ($\pm$ SD) (m)	Mean ($\pm$ SD) (m)		Mean ($\pm$ SD) (m)	Mean ($\pm$ SD) (m)	
Discharge	86.1($\pm$ 126.5)	53.6 ($\pm$ 78.4)	0.39	206 ($\pm$ 195.74)	91.3 ($\pm$ 55.3)	0.38
1- month	149.8 ($\pm$ 171.2)	152 ($\pm$ 175.8)	0.97	332 ($\pm$ 182.1)	212 ($\pm$ 97.1)	0.37
3- months	151.5 ($\pm$ 179.6)	135.5 ($\pm$ 192.9)	0.81	332 ($\pm$ 182.1)	212 ($\pm$ 97.1)	0.37

*Values expressed as mean ($\pm$ SD), m - metres; ITT - intention to treat; PP - per protocol.

Participants in the intervention group had a greater increase in mean distance walked from the time of hospital discharge to three months after discharge (81.9m) compared to those in the control group (65.4m) using the ITT analysis. With per protocol analysis, the intervention group had an increase of 120.7m in mean distance walked with the 6MWT from hospital discharge to one month after discharge and the control group had an increase of 126m. No statistically significant differences in mean distance walked with the 6MWT was observed between the groups at the various time points when the ITT and per protocol analyses were performed.

The ANCOVA was performed to evaluate the difference in the distance walked in metres between the two groups over time. No statistical significance was noted when the ITT analysis was performed ($p=0.76$). Similarly for the per protocol analysis ($p=0.22$).

4.4.2 Actual 6MWT Distance Achieved versus Predicted Distance for the 6MWT

The ANOVA was performed to compare the difference in the predicted percentage walked as measured by the 6MWT between the two groups at specified time points. The equation used to determine the predicted distance walked was $6MWD = (2 \times \text{height}) - (2.29 \times \text{weight}) - (5.78 \times \text{age}) + 667\text{m}$ (Enright and Sherrill, 1998). Table 4.8 provides a summary of results for both ITT and per-protocol analyses.

Table 4.9: Comparison of the Percentage of Predicted Distance Walked within the Participating Groups Over Time

6MWT (Percentage of Predicted distance)	ITT			PP		
	Control (n=14)	Intervention (n=16)	p Value	Control (n=3)	Intervention (n=3)	p Value
	Mean ($\pm$ SD) (%)	Mean ($\pm$ SD) (%)		Mean ($\pm$ SD) (%)	Mean ($\pm$ SD) (%)	
Discharge	31.9 ($\pm$ 38.9)	16.3 ($\pm$ 23.2)	0.19	68.2 ($\pm$ 49)	29.8 ($\pm$ 14))	0.85
1- month	42 ($\pm$ 50.1)	44.6 ($\pm$ 46.9)	0.88	120.4 ($\pm$ 28.7)	75 ($\pm$ 38.7)	0.72
3- months	41.7 ($\pm$ 52.5)	41 ($\pm$ 52.5)	0.97	120.4 ($\pm$ 28.8)	75.3 ($\pm$ 38.8)	0.73

*Values expressed as mean ($\pm$ SD); 6MWT - six minute walk test; ITT - intention to treat; PP - per protocol.

At the time of discharge from hospital, the control group was able to achieve 31.9% of their predicted distance walked on the 6MWT compared to 16.3% of the predicted distance walked in the intervention group using ITT analysis. At one month after discharge the intervention group achieved a greater improvement in percentage of predicted distance walked (28.3%) than the control group (10.1%). At three months after discharge participants in both groups were able to achieve approximately 41% of their predicted distance for the 6MWT. Per protocol analysis shows that those participants who completed the trial in the control group were able to achieve a larger percentage of their predicted distance walked between discharge and one month compared to those who completed the trial in the intervention group. There was no statistically significant difference noted in percentage of predicted distance achieved on the 6MWT between the groups at each time point using either method of data analysis.

The comparison between the groups over time when the ANCOVA was performed resulted in no statistical significance for the ITT analysis ($p=0.57$). When the same was applied for the per protocol analysis no statistical significance was observed ($p=0.86$).

4.5 THE EFFECT OF INSPIRATORY MUSCLE TRAINING ON THE ABILITY TO PERFORM ACTIVITIES OF DAILY LIVING

The HAQ tool was used to evaluate the performance of ADL. A lower self-rating score implied that the participant could perform their ADL's, however a higher score indicated their inability or difficulty in performing ADL's (Bruce and Fries, 2003).

The ANOVA was performed to evaluate the difference in self rating scores between the two groups. Table 4.9 provides a summary of the results for the ITT and per protocol data.

Table 4.10: A Comparison of HAQ Scores between Participant Groups at Specified Time Points

HAQ Score	ITT			PP		
	Control (n=14)	Intervention (n=16)	p Value	Control (n=3)	Intervention (n=3)	p Value
	Mean ($\pm$ SD)	Mean ($\pm$ SD)		Mean ($\pm$ SD)	Mean ($\pm$ SD)	
Extubation	3.2 ($\pm$ 4.2)	12.5 ($\pm$ 7.4)	0.00	4 ($\pm$ 4)	16.6 ($\pm$ 3.5)	0.01
Discharge	2 ($\pm$ 1.9)	7.1 ($\pm$ 7.6)	0.02	2.3 ($\pm$ 1.5)	4.6 ($\pm$ 6.4)	0.57
1- month	1.7 ($\pm$ 2)	7.2 ($\pm$ 7.3)	0.01	1.3 ($\pm$ 1.5)	3 ($\pm$ 3)	0.44
3- months	1.4 ($\pm$ 2)	6.2 ($\pm$ 7.5)	0.02	0 ($\pm$ 0)	1.6 ($\pm$ 2)	0.23

*Values expressed as mean ($\pm$ SD); HAQ - health assessment questionnaire, ITT - intention to treat; PP - per protocol

The intervention group had higher HAQ scores than the control group from the extubation period until the three month period for the ITT and per protocol analysis. At extubation the difference between the groups was statistically significant for the ITT analysis ($p=0.00$) and per protocol analysis ($p=0.01$). A statistical significance was observed at the discharge period for the ITT analysis ($p=0.02$), however this was not the case when per protocol analysis was performed. At one month after discharge the ITT analysis yielded a statistical significance ($p=0.01$) when the two groups were compared. This result was not the same when per protocol analysis was evaluated because no statistical significance was observed. At three months the control group had the lowest score of zero when per protocol analysis was applied, however there was no statistical significance observed between the groups ($p=0.23$). However, a statistical significance when the ITT analysis was found ($p=0.02$).

The ANCOVA compared the HAQ scores between the two groups over time. The comparison between the groups over time when the ANCOVA was performed resulted in no statistical significance for the ITT analysis ($p=0.29$). When the same was applied for the per protocol analysis no statistical significance was observed ($p=0.54$).

4.6 THE EFFECT OF INSPIRATORY MUSCLE TRAINING ON QUALITY OF LIFE AS MEASURED BY THE EQ-5D

4.6.1 The Effect of Inspiratory Muscle Training on the Health Percentage (VAS) as Measured by the EQ-5D

The visual analogue scale (VAS) is a component of the EQ-5D that evaluates the participant's health percentage rating. A lower percentage would indicate a decreased rate in the state of health and a higher rating indicates an increased health state (Brooks, 1996).

The ANOVA was performed to evaluate the difference in quality of life between the two groups. Table 4.10 provides a summary of the results for the ITT and per protocol data.

Table 4.11: A Comparison of Quality of Life as Measured with the EQ-5D VAS within the Participant Groups at the Specified Time Points

EQ5D (VAS)	ITT			PP		
	Control (n=14)	Intervention (n=16)	p Value	Control (n=3)	Intervention (n=3)	p Value
	Mean ($\pm$ SD) (%)	Mean ($\pm$ SD) (%)		Mean ($\pm$ SD) (%)	Mean ($\pm$ SD) (%)	
Extubation	57 ($\pm$ 33.4)	69 ($\pm$ 17.3)	0.21	66.6 ($\pm$ 28.8)	63.3 ($\pm$ 11.5)	0.86
Discharge	55.7 ($\pm$ 35.5)	78.1($\pm$ 25.6)	0.05	65 ($\pm$ 13.2)	73.3 ($\pm$ 27.5)	0.66
1- month	64.6 ($\pm$ 38.9)	75.3 ($\pm$ 31.3)	0.41	86.6 ($\pm$ 15.2)	86.6 ($\pm$ 11.5)	1.00
3- months	65.7 ($\pm$ 39.4)	70.9 ($\pm$ 37.2)	0.71	91.6 ($\pm$ 10.4)	93.3 ($\pm$ 7.6)	0.83

*Values expressed as mean ($\pm$ SD); EQ-5D - European quality of life 5-dimension; ITT - intention to treat; PP - per protocol.

At the time of extubation the intervention group had achieved a 69% health rating when the ITT data was analysed as compared to 57% in the control group, however no statistical significance was observed between the groups. The same applied to the per protocol data analysis. The health percentage rating had decreased to 55.7% in the control group and increased to 78.1% in the intervention group for the ITT analysis at the discharge time period. A statistical significance was observed ($p=0.05$) between the two groups but per protocol analysis did not yield the same result. The control group had a gradual increase in VAS at one and three months after discharge, however no statistical significance was observed for the ITT and per protocol analysis.

Similarly when the ANCOVA was performed to compare the effects of the intervention over time, the results for the ITT analysis were not statistically significant ($p=0.23$). The same result was found with the per protocol analysis ($p=0.33$).

4.6.2 The Effect of Inspiratory Muscle Training on the Quality of Life Domains as Measured by the EQ-5D

The EQ-5D domains evaluate five different aspects of quality of life. These are the ability to mobilise, to perform self-care and to perform usual activities of daily living including work and leisure activities, establishes the presence of pain and anxiety or depression.

Table 4.11 summarises the results for per protocol data analysis regarding the categorical data obtained for the various domains of the EQ-5D.

Table 4.12: A comparison of Quality of Life Domains as Measured with the EQ-5D within the Participant Groups at the Specified Time Points

EQ-5D Domains	At Discharge		At Three Months after Discharge	
	Control Group n= 3	Intervention Group n= 3	Control Group n= 3	Intervention Group n= 3
Mobility:				
▪ No Problem	n= 0 (0%)	n= 2 (66.7%)	n= 3 (100%)	n= 3 (100%)
▪ Problem	n= 3 (100%)	n= 1 (33.3%)	n= 0 (0%)	n= 0 (0%)
Self-Care:				
▪ No Problem	n= 3 (100%)	n= 2 (66.7%)	n= 3 (100%)	n= 3 (100%)
▪ Problem	n= 0 (0%)	n= 1 (33.3%)	n= 0 (0%)	n= 0 (0%)
Usual Activities:				
▪ No Problem	n= 2 (66.7%)	n= 1 (33.3%)	n= 3 (100%)	n= 2 (66.7%)
▪ Problem	n= 1 (33.3%)	n= 2 (66.7%)	n= 0 (0%)	n= 1 (33.3%)
Pain/Discomfort:				
▪ No Problem	n= 0 (0%)	n= 1 (33.3%)	n= 3 (100%)	n= 2 (66.7%)
▪ Problem	n= 3 (100%)	n= 2 (66.7%)	n= 0 (0%)	n= 1 (33.3%)
Anxiety/Depression:				
▪ No Problem	n= 2 (66.7%)	n= 1 (33.3%)	n= 3 (100%)	n= 3 (100%)
▪ Problem	n= 1 (33.3%)	n= 2 (66.7%)	n= 0 (0%)	n= 0 (0%)

*Values expressed as numbers (percentages); EQ-5D: European quality of life 5-dimension.

The mobility domain and function was reportedly not a problem for the control group at the time of discharge from the hospital and three months after discharge. One participant in the intervention group had a problem with the ability to mobilise. At the three month follow-up point, all participants in the intervention group had no problems with the ability to mobilise. The ability to attend to self-care functions was noted as a problem amongst one participant in the intervention group at discharge. However, this had improved at the three month follow-up point. Some participants in the intervention group [n=2 (66.7%)] reportedly had problems with the ability to perform functions pertaining to usual activities at the time of discharge from hospital, compared to only one participant (33.3%) in the control group. This factor had markedly improved at the three month follow-up point. Pain and discomfort was reportedly 'a problem' or present for all participants in the control group (100%) at the discharge period. Two participants (66.7%) in the intervention group also had problems with pain during this period. This factor had improved for both the control and intervention groups at the three month follow-up assessment. The intervention had a greater number of participants, n= 2 (66.7%) who reported that they could be

anxious or depressed at the discharge time points as compared to the control group, $n=1$ (33.3%). At the three month follow-up point both groups had reported no problems with regards to feelings of anxiety and depression.

CHAPTER 5

5. DISCUSSION

To the best of the researcher's knowledge, this is the first study of its kind to investigate the effect of inspiratory muscle training on re-intubation rate of patients with critical illness. Inspiratory muscle training did not result in a significant difference in re-intubation rate between the two groups as only one participant needed to be re-intubated throughout the duration of the trial. Inspiratory muscle training did seem to have an influence on expiratory muscle strength in the intervention group at the time of discharge from hospital and it seemed to slow the rate of deterioration in inspiratory muscle strength from extubation to the three month follow-up for those in the intervention group. Even though the estimated sample size for the trial was met, there was a high dropout rate after discharge from the hospital. As a result more focus will be placed on the ITT data analysis in this discussion to prevent bias in reporting the effect of IMT intervention (Shah, 2011).

The greater number of participants was males ($n=21$) as compared to females ($n=9$), with most males ($n=10$) diagnosed with trauma related injuries than females ($n=0$). Males are generally inclined to incur trauma more than females. This observation was noted in a study by Van Aswegen et al. (2010) where 40 out of 42 survivors of penetrating trunk trauma were male. The majority of the patients admitted for the current study had a medical or surgical related diagnosis. Clark and Lettieri (2013) inferred that prolonged MV is more prevalent in a medical ICU. Therefore, resulting in a higher mortality rate as compared to the surgical or trauma related diagnoses (Clark and Lettieri, 2013; Shosbree et al., 2013). Although this study did not evaluate the effect of diagnosis on LOS, it was noted that the mean duration of MV for the whole group of participants was 6.2 days ($\pm$ SD 8.6) and the intervention group had a longer duration on MV than the control group. The MV days were substantially lower than the 10.2 ± 10.8 days reported by Clark and Lettieri (2013), for a similar population with regards to diagnosis type.

The control group participants were significantly older than the intervention group participants ($p=0.05$) that had a significantly lower APACHE II score than those in the control group ($p=0.04$). Literature states that a high APACHE II score results in an increased duration of MV (Clark and Lettieri, 2013). However, this was not the case in this study. Although the control group had a higher predicted risk of mortality on

the APACHE II score they had 4.2 days on MV, 5.2 days in ICU and 10 days hospital LOS in comparison to 7.6 days on MV, 9.3 days in ICU and 38 days hospital LOS for the intervention group participants. The participants who required MV for more than seven days and a prolonged ICU stay incur muscle weakness and are easily fatigued. This further hampers functional outcomes after ICU stay and results in a lengthy recovery period (Skinner et al., 2008). It is possible that the intervention group acquired more complications as a result of critical illness than the control group but, due to the study design, the extent of these factors was not measured. The APACHE II and SAPS II scores are tools used to predict mortality on admission to ICU and are not suitable to evaluate morbidity associated with critical illness. A limitation of this study is that the sequential organ failure assessment (SOFA) tool, which assesses morbidity, was not considered as an outcome measure.

The difference between the control and intervention group in relation to the the number of participants who were HIV positive was statistically significant ($p=0.02$). However, there is a difference of one patient between the control and intervention group, thus although statistically significant, it bears no clinical significance. The effects of HIV might have had an impact on physical ability, however the results of this study may have been influenced by the impact of critical illness on physical ability. The ability to perform ADL's as measured by the HAQ was markedly decreased in the intervention group throughout the different time points as they scored higher which indicated their inability to perform certain tasks. This resulted in a significant difference between the groups at each time point the ITT analysis was performed. These findings support the assumption that participants in the intervention group may have experienced higher levels of morbidity due to critical illness and HIV status than those in the control group even though those in the control group had a higher risk of mortality on admission to ICU.

As mentioned earlier, inspiratory muscle training did not have a significant influence on re-intubation rate as only one participant in this trial needed to be re-intubated. Literature has reported on numerous weaning protocols and the goal to reduce extubation failures through careful planning and identification of patients who are at risk of failing extubation (Cavallone and Vannucci et al., 2013; Planı et al., 2013). It has been reported in numerous studies that an ineffective weaning programme would result in extubation failure and thus re-intubation (Cox, 2012). The reasons pertaining to the decreased need for re-intubation observed in this study could be attributed to the sound weaning practices in the ICU that participated in this study. This was a

factor that was unknown to the researcher at the start of the trial as no research had previously been conducted on weaning and extubation practices in these ICU. The researcher is of the opinion that the physiotherapy treatment administered in this study, with or without the IMT, was specific to the individual participant's impairments as recommended by other researchers (Skinner et al., 2008; Ambrosino et al., 2012). The control group received physiotherapy treatment only and no participant required re-intubation. Physiotherapy interventions have been shown to improve general muscle strength, function as measured by the 6MWT and overall QOL (Skinner et al., 2008; Ambrosino et al., 2012; Castro et al., 2013) and therefore the researcher concludes that the standard in-hospital physiotherapy treatment given was adequate to assist patients in their recovery.

The use of IMT has been reported to increase PiMax by 8cmH₂O (Moodie et al., 2011), however such an improvement was not observed in this study. The ITT analysis showed no statistically significant difference in PiMax between the control and intervention groups at any of the time points that it was measured. There was however a smaller decline in mean PiMax over time in the intervention group (2.4cmH₂O) compared to the control group (9.1cmH₂O). Even though there was no statistically significant difference between the groups, it might be seen as a clinically significant finding. Therefore it is reasonable to assume that IMT could have had a protective effect on inspiratory muscle strength. The observed decline in PiMax instead of increase in PiMax could be ascribed to the protocol for progression of IMT treatment for this RCT. In this study the initial load of 30% of PiMax was increased only when the participant was able to perform the training for 30 minutes. During retrospective review of the research assistants notes it was however discovered that through the training period the IMT load was increased by less than 10%. The reasons documented by the research assistants included patient fatigue, dizziness or shortness of breath after IMT which contributed to a more conservative increment in IMT threshold. Another reason stated by the research assistants was that the period from commencement of IMT to the time of participant discharge from hospital was too short to increase the IMT training substantially. A similar restriction to IMT therapy was reported by Chang et al. (2005). Therefore, the researcher has to conclude that the pressure or overload that was applied during IMT in this RCT was not challenging enough to produce neural changes to increase PiMax significantly (Romer and McConnell, 2002; McConnell, 2013). There are no set guidelines for IMT threshold training. Some researchers such as Sprague et al. (2003) and Bissett et al. (2007) used an initial IMT threshold load of 50% of PiMax administered once a day.

The increased load resulted in marked improvements in PiMax and all patients were successfully weaned from MV (Sprague et al., 2003; Bissett et al., 2007). Other researchers increased the load by 10% each session until a maximal 40% was attained (Cader et al., 2010). Martin et al. (2011) initiated training at the highest tolerable pressure, the number of breaths performed per set was increased to progress the treatment. Chang et al. (2005) used the BORG scale reading as an indicator for the initial intensity and that it could be increased when the IMT was performed on extubated patients. Therefore literature reports that the initial intensity or load varies between 30 to 50% and the highest tolerable pressure. Progression was thus incited by increasing the number of breaths, assessing BORG scale, increasing the intensity at each session or in the case of this study the ability to perform the IMT over a specified period of time. There are varying methods of training and that could be the reason for the inconsistencies in results reported from IMT training interventions.

There was marked improvement of the PeMax and this was statistically significant at the time of discharge for the ITT ($p=0.02$) and per protocol ($p=0.05$) analyses. A 27.3cmH₂O mean difference in PeMax was observed at discharge between the intervention and control group. The intention of the IMT intervention was to increase inspiratory muscle strength (negative pressure), however this study showed improvement of expiratory muscle strength (positive pressure). It is reasonable to assume that strength training of the inspiratory muscles would lead to an increase in tidal volume. As lung volume increases, the internal intercostal muscles, responsible to expiration, would be placed in a stretched position and would be able to contract more forcefully during expiration which would facilitate a more forceful peak expiratory flow rate and therefore a higher PeMax reading. Condessa et al. (2013) investigated the effect of IMT on rate of weaning of patients from MV. These authors also found improvements in PeMax in the group that performed IMT training and postulated that this finding was a result of IMT training on the strength of the intercostal muscles. The process of coughing requires the use of expiratory muscle contraction and the inability to cough or clear secretions has been identified as one of the factors that may predispose patients to fail extubation and increase the need for re-intubation (Khamiees et al., 2001; Thille et al., 2013). Therefore assessment of PeMax seems to be an important factor in the management of patients prior to and after extubation. Unfortunately IMT did not seem to have a carryover effect on PeMax after discharge from the hospital in the current study.

The effects of critical illness have been reported to transcend beyond ICU (Chang et al., 2005) and hospital stay (Puthuchearry et al., 2013). Factors such as dyspnoea, decreased exercise tolerance, inadequate performance of ADL's and decreased sense of QOL have been identified as hindrances to full recovery (Feng et al., 2009; Kelly and McKinley, 2010; Elliot et al., 2011). These factors are intertwined and do not necessarily function independently (Kelly and McKinley, 2010; McConnell, 2013). McConnell (2013) reported that the presence of disease would affect the demand and capacity ratio for oxygen which results in dyspnoea and failure to supply both the peripheral and respiratory muscles with adequate amounts of oxygen. The current study did not yield a statistical significance between the two groups when the perceived level of breathlessness was measured with the BORG scale at the different time points. The ITT analysis showed relatively low mean BORG scale readings for participants in both groups at extubation. At three months follow up the intervention group still had a slightly higher level of perceived breathlessness compared to the control group. This seems like a contradiction in light of the fact that the intervention group had a smaller decline in PiMax over time. To quantify and objectively rate the perception of breathlessness has been proven to be difficult because it is subjective and thus unique to each individual (Nicholls, 2000). The use of IMT did not result in a statistically significant decrease in the perceived level of shortness of breath for the ITT ($p=0.73$) or per protocol ($p=0.45$) analysis over time. This study reported on the values pertaining to the BORG scale as expressed by the participants. Other researchers report a baseline or cut off score for perceived level of breathlessness with the BORG scale for example the score of six (Chang et al., 2005). It is difficult to deduce what the acceptable level of perceived breathlessness is due to the subjectivity of this measurement tool but it is reasonable to conclude that a lower BORG scale score is better than a higher score.

Participants in the intervention group were only able to achieve 16.3% of their predicted distance walked with the 6MWT at the time of discharge from hospital. Over time these participants managed to increase the mean distance walked by 81.9m to achieve a mean of 41% of predicted distance walked at three months. The control group achieved 31.9% of the predicted distance walked at the time of discharge from hospital. Over time they managed to increase the mean distance walked by only 65.4m to achieve a mean of 41.7% of predicted distance walked by three months. The IMT training did not have any significant influence on distance walked or percentage of predicted distance walked with the 6MWT over time. The low percentage of predicted distance walked at discharge seems to support the

assumption that the intervention group had a higher morbidity than the control group during their hospital stay. Furthermore, the distance walked reportedly increases in ARDS survivors at the one year follow up (Herridge et al., 2003). However, the predicted percentage of distance walked is lower due to the self-reported feelings of muscle wasting and weakness (Herridge et al., 2003) which could have been the case in the current study. The inability to independently function in society is one of the ramifications of surviving critical illness and may result in disability (Davydow et al., 2008; Feng et al., 2009; Latronico and Bolton, 2011; Puthuchearry et al., 2013) and a reduction in exercise tolerance. The 6MWT is one such measurement that evaluates the ability to perform functional activities after critical illness (Chang et al., 2005; Elliot et al., 2011). Herridge et al. (2011) reports on a study that evaluated 6MWT in ARDS survivors between the three months and five years follow-up periods. The researchers found that younger participants who survive ARDS recover quicker than the older patients (Herridge et al., 2003). However, the resultant functional outcomes are still affected at the five year follow-up period (Herridge et al., 2003; Herridge et al., 2011). The resultant muscle weakness and inability to return to the pre-admission state have been identified as reasons for this (Herridge et al., 2011). Thus this concurs with the results of this study. Although the follow-up process was not as lengthy, the participants in the intervention group were younger and a lower functional status was measured for this group with the 6MWT.

As mentioned earlier, the intervention group had a higher HAQ score than the control group. These findings are in conflict with the results reported by other researchers on the marked improvement of the performance of ADL's when IMT is performed (Chang et al., 2005). This group had a lengthier stay on MV, in ICU and hospital, which could have led to decreases in general muscle strength and resultant fatigue as reported by Winkelman (2009). As a result these participants might have felt more restricted to perform their daily activities; thus supporting the finding of other researchers that six months after discharge from ICU, patients were still reliant on assistance from others for their ADL's as measured by the KATZ scale (Albeha et al., 2007; Kelly and McKinley, 2010). The HAQ questionnaire has been reported to evaluate the effects of disability and the resultant relation to mortality (Bruce and Fries, 2003).

The 6MWT and ADL performance are often matched because one would alter the other, as the 6MWT measures performance and the ADL evaluates behaviour (Shoemaker et al., 2013). Therefore the outcomes do not operate independently and

this has a resultant impact on QOL which include the inherent emotional and mental factors, five years after surviving critical illness (Herridge et al., 2011). The pre-admission HRQOL reduces in patients who were admitted into the ICU for 48 hours and more in comparison to patients who are admitted for fewer hours (Hofhuis et al., 2008). For example a shorter duration of stay in ICU has been reported to result in better QOL outcomes in survivors of penetrating trunk trauma (Van Aswegen et al., 2011). Other factors such as type of diagnosis seem to have an impact on QOL. Patients diagnosed with a trauma related ailment are reportedly likely to still have residual pain or discomfort as compared to other patients (Dowdy et al., 2005). This study did not evaluate the difference between the types of diagnosis and the resultant pain or discomfort. However, the study observed that 37.5% of the participants in the intervention group had a trauma related ailment as compared to 28.6% of the participants in the control group. When the EQ-5D health percentage (VAS) was performed, the participants in the intervention group reportedly felt that their health status was higher and more improved than the control group at the one month follow up assessment. This yielded a statistical significance between the groups at the discharge period ($p=0.05$). The researcher is of the opinion that cultural perception might have influenced some participants' responses. Even though some participants reported a higher VAS score because they felt their condition had improved, others might have reported a higher score to avoid being kept in hospital for a longer duration and therefore to relay the impression that they were better. This is a subjective observation made by the researcher and is supported by her clinical experience in this hospital. The intervention group had a longer LOS in hospital, so they would not report a result that may hamper their efforts to leave the hospital. The use of IMT did not improve the health perception percentage (EQ-5D VAS) over time for both the control or intervention group. The specific domains of the EQ-5D questionnaire set out to evaluate the impact of critical illness on the participants QOL. In the intervention group, 66.7% of participants reported problems in all domains namely usual activities, pain or discomfort and anxiety or depression at the time of discharge from the hospital. A considerable number of participants in this group had a trauma related diagnosis which resulted in pain that could have resulted in this low QOL score at discharge as well as their poor ability to perform the 6MWT (16.3%). At the three month period the control group reported no problems with any of the domains of the EQ-5D. However, some participants in the intervention group still reported problems with usual activities and pain or discomfort.

5.1 LIMITATIONS OF THE CURRENT STUDY

- The physiotherapy and IMT intervention did not begin on the day of extubation, so this could have influenced the results obtained.
- The current setting being Charlotte Maxeke Academic Johannesburg Hospital is a specialist hospital so most patients admitted are usually stabilised and treated. Thereafter, they are transferred back to their referring hospitals. The fast patient turnover rate at this hospital only became apparent during the data collection phase of the study. This became a challenge, as patients were tracked till the date of extubation and some were assessed. However some were discharged or transferred before any physiotherapy intervention could be administered.
- Although explanation with regards to the study were given, the trauma experienced and effects of ICU stay resulted in some participants not consenting or agreeing to take part in anything that resulted in them staying in hospital.
- There was a high dropout rate and loss to follow-up, as described on the flowchart (Figure 4.1). Only 20% of the study population completed the study. The probable reasons for this high rate could be that the participants deemed themselves healthy and did not require further medical intervention; similar to the situation reported by Van Aswegen et al. (2010). Studies have stated that research with long follow up periods often result in an increased dropout rate (Adamson and Elliot 2005). Another reason was that although the participants lived and worked in Johannesburg, they had homes or support in Limpopo, Mpumalanga and Kwazulu-natal province, and Zimbabwe. Some participants opted to go back to a supportive environment for the duration of their recovery. So by the time the person felt strong enough to return to Gauteng, the three month period had lapsed or their condition had become worse and they required re-admission usually in other hospitals. Although some participants were re-recruited after they had missed an assessment for a certain period, this was not the case for most of the participants.
- Methods utilized to improve follow up of participants after hospital discharge:
 - Patients were given a copy of the research and appointment information (Appendix 16).

- Participants were called at least two weeks before their scheduled follow up appointments to remind them to attend.
- For those who did not have a mobile phone at the time of discharge, the alternative number of a family member or friend was recorded to be used for follow up reminders.
- The researcher sought the advice of the hospital administrative staff for contact details of other family members of a participant if that participant could not be reached on the numbers provided at the time of hospital discharge.
- Appointments were scheduled in the same week as participants' appointments for ICU follow up consultations.
- The rapid changeover of research assistants was also of concern. Reasons for changeover varied from unplanned resignations to annual, sick or maternity leave. Therefore when the researcher had assessed the patient the research assistants would be unavailable thus treatment for the day would be forfeited. Research assistants reported that the treatment plans were time consuming and at times the patients battled to do both the physiotherapy and IMT intervention efficiently in one session. Lack of support for the study from ICU unit heads was also experienced. Although they were briefed about the aims and purposes of the study they were not always willing to complete the temporary consent form for inclusion of patients in this trial.
- The experience of the use of IMT by the participants was not documented. This would assist in planning for better instructions that could assist the researcher to increase load of training possibly at a faster rate.

5.2 RECOMMENDATIONS FOR FUTURE RESEARCH

- PiMax/PeMax could be assessed prior to extubation as this would help ascertain whether a patient is at high risk for re-intubation and pre-emptive measures would be identified. The data collection procedure could be revised so that the participant does not tire on the day of extubation and treatment can commence then. For example PiMax/PeMax and BORG scale could be evaluated on the day

of extubation, and the rest of the outcome measures would be assessed thereafter (over a few more days).

- A multicentre study should be conducted to aid in patient recruitment and retention of participants during the follow-up period.
- The hospital selected for a study that aims to evaluate the effects of IMT after extubation should have a low patient turnover rate.
- Introduce and work in conjunction with the dieticians when physiotherapy interventions that aim to increase and improve muscle strength are planned. It is known that muscle mass and general body weight reduces in patients recovering from critically illness. Optimising nutrition and supplementation would assist in increasing muscle mass and energy.
- Research that focuses on the effects of morbidity on the overall function of a patient after critical illness.
- To have a research team that stays the same for the duration of the study.
- Baseline measurements should include the assessment of pain, discomfort and orientation.

CHAPTER 6

6. CONCLUSION

The results of this study support the null hypothesis that states that there is no difference in patient re-intubation rate after extubation following critical illness and prolonged MV, when IMT is added to standard in-hospital physiotherapy rehabilitation. The IMT intervention seemed to have a protective effect over deterioration in inspiratory muscle strength in the intervention group although this was not statistically significant. The inconsistencies in the administration of IMT intervention programmes and the high dropout rate during the duration of this study could have led to the results not being statistically significant for most outcome measures. The role and importance of physiotherapy treatment during hospitalisation was highlighted in this study, as control group participants, who initially had a higher risk of mortality had improved outcomes in relation to the intervention group participants who had a lower risk of mortality on admission to ICU.

REFERENCES

- Abilés, J., de la Cruz, A.P., Castaño, J., Rodríguez-Elvira, M., Aguayo, E., Moreno-Torres, R., Llopis, J., Aranda, P., Argüelles, S., Ayala, A., de la Quintana, A.M. and Planells, E.M. Oxidative stress is increased in critically ill patients according to antioxidant vitamins intake, independent of severity: a cohort study. *Critical Care*, 2006, vol 10, no 5, pp 1-9.
- Adamson, H. and Elliot, D. Quality of life after a critical illness: a review of general ICU studies 1998-2003. *Australian Critical Care*, 2005, vol 18, no 2, pp 50-60.
- Aitken, L.M., Burmeister, E., McKinley, S., Alison, J., King, M., Leslie, G. and Elliot, D. Physical recovery in intensive care unit survivors: a cohort analysis. *American Journal of Critical Care*, 2015, vol 24, no 1, pp 33-40.
- Akgün, K.M., Pisani, M. and Crothers, K. The changing Epidemiology of HIV-infected Patients in the Intensive Care Unit. *Journal of Intensive Care Medicine*, 2011, vol 26, no 31, pp 151-164.
- Albeha, F.J., Santos, C.C., Maia, P.C., Castro, M.A. and Barros, H. Quality of life after stay in surgical intensive care unit. *BioMed Central Anesthesiology*, 2007, vol 7, no 8, pp 1-12.
- Ambrosino, N., Venturalli, E., Vaghegghini, G., and Clini, E. Rehabilitation, weaning and physical therapy strategies in chronic critically ill patients. *European Respiratory Journal*, 2012, vol 39, pp 487-492.
- Amidei, C. Measurement of physiological responses to mobilisation in critically ill adults. *Intensive and Critical Care Nursing*, 2012, vol 28, no 2, pp 58-72.
- Bisset, B., Leditschke, I.A., Green, M. Specific inspiratory muscle training is safe in selected patients who are ventilator-dependant: A case series. *Intensive and Critical Care Nursing*, 2012, vol 128, pp 98-104.
- Bisset, B., Leditschke, I.A., Neeman, T., Boots, R. and Paratz, J. Weaned but weary: One third of adult intensive care patients mechanically ventilated for and days or more have impaired inspiratory muscle endurance after successful weaning. *Heart and Lung*, 2015, vol 44, pp 15-20.
- Boles, J-M., Bion, J., Connors, A., Herridge, M., Marsh, B., Melot, C., Pearl, R., Silverman, H., Stanchina, M., Vieillard-Baron, A. and Welte, T. Weaning from mechanical ventilation. *European Respiratory Journal*, 2007 vol 29, no 5, pp 1033-1056.
- Bourdin, G., Barbier, J., Burle, J-F., Durante, G., Passant, S., Vincent, B., Badet, M., Bayle, F., Richard, J-C., and Guérin, C. *Respiratory Care*, 2010, vol 55, no 4, pp 400-407.
- Brooks, R. EuroQOL: the current state of play. *Health Policy*, 1996, vol 37, no 1, pp 53-72.
- Bruce, B. and Fries, F. The Stanford health assessment questionnaire: a review of its history, issues, progress and documentation. *The Journal of Rheumatology*, 2003, vol 30, no 1, pp 1-6.
- Bruton, A., Conway, J.H. and Holgate, S.T. Inspiratory muscle dysfunction after prolonged periods of mechanical ventilation: Two case studies. *Physiotherapy*, 2002, vol 88, no 3, pp 131-137.
- Cader, S.A., de Vale, R.G.S., Castro, J.C., Bacelar, S.C., Biehl, C., Gomes, M.C.V., Cabrera, W.E. and Dantas, E.H.M. Inspiratory muscle training improves maximal inspiratory pressure and may assist weaning in older intubated patients: a randomised trial, *Journal of Physiotherapy*, 2010, vol 56, pp 171-177.

- Castro, A.A.M., Calil, S.R., Freitas, S.A., Oliveira, A.B. and Porto, E.F. Physiotherapy effectiveness to reduce hospitalization and mechanical ventilation length of stay, pulmonary infection rate and mortality in ICU patients. *Respiratory Medicine*, 2013, vol 107, pp 68-74.
- Carpené, N., Vagheggini, G., Panait, E., Gabbrielli, L. and Ambrosino, N. A proposal of a new model for long-term weaning: Respiratory intensive care unit and weaning center. *Respiratory Medicine*, 2010, vol 104, pp 1505-1511.
- Caruso, P., Denari, S.D.C., Ruiz, S.A.L., Bernal, K.G., Manfrin, G.M., Friedrich, C., and Deheinzelin, D. Inspiratory muscle training is ineffective in mechanically ventilated critically ill patients. *Clinics*, 2005, vol 60, no 6, pp 479-484.
- Cavallone, L.F. and Vannucci, A. Extubation of the Difficult Airway and Extubation Failure. *Anesthesia and Analgesia*, 2013, vol 116, no 2, pp 368-383.
- Chang, A.T., Boots, R.J., Henderson, R., Paratz, J.D. and Hodges, P.W. Case Report: Inspiratory muscle training in critically ill patients-a report of two cases. *Physiotherapy Research International*, 2005, vol 10, no 4, pp 222-226.
- Chang, A.T., Boots, R.J., Brown, M.G., Paratz, J. and Hodges, P.W. Reduced Inspiratory Muscle endurance following successful weaning from prolonged mechanical ventilation. *Chest*, 2005, vol 128, no 2, pp 553-559.
- Chiappa, A.R., Roseguini, B.T., Vierra, P.J.C., Alves, C.N., Tavares, A., Winkelmann, E.R., Ferlin, E.L., Stein, R., and Ribeiro, J.P. Inspiratory Muscle training improves blood flow to resting and exercising limbs in patients. *Journal of American College of Cardiology*, 2008, vol 51, no 17, pp 1663-1671.
- Clark, P.A. and Lettieri, C.J. Clinical model for predicting prolonged mechanical ventilation. *Journal of Critical Care*, 2013, vol 28, pp 880.e1-880.e7.
- Clini, E. and Ambrosino, N. Early physiotherapy in the respiratory intensive care unit. *Respiratory Medicine*, 2005, vol 99, pp 1096-1104.
- Condessa, R.L., Brauner, J.S., Saul, A.L., Baptista, M., Silva, A.C.T. and Vieira, S.R.R. Inspiratory muscle training did not accelerate weaning from mechanical ventilation but did improve tidal volume and maximal respiratory pressures: A randomised trial. *Journal of Physiotherapy*, 2013, vol 59, no 2, pp 101-107.
- Cox C.E. Systemic inflammation in chronic critical illness. *Respiratory Care*, 2012, vol 57, no 6, pp 859-868.
- Crimi, E., Sica, V., William-Ignerro, S., Zhang, H., Slutsky, A.S., Ignarro, L.J. and Napoli, C. Role of oxidative stress in experimental sepsis and multisystem organ dysfunction. *Free Radical Biology and Medicine*, 2006, vol 40, pp 398-406.
- Crossingham, G. and MacNaughton, P. The long-stay ICU patient. *Anaesthesia and Intensive Care Medicine*, 2009, vol 10, no 4, pp 179-182.
- Davydow, D.S., Giffard, J.M., Desai, S.V., Needham, D.M. and Bienvenu, O.J. Posttraumatic stress disorder in general intensive care unit survivors: A systematic review. *General Hospital Psychiatry*, 2008, vol 30, pp 421-434.
- Denehy, L., Skinner, E.H., Edbrooke, L., Haines, K., Warrillow, S., Hawthorne, G., Gough, K., Vander Hoom, S., Morris, M.E. and Berney, S. Exercise rehabilitation for patients with critical illness: a randomized controlled trial with 12 months of follow-up. *Critical Care*, 2013, vol 17, no 4, pp 1-12.
- Dellinger, R.P., Levy, M.M., Carlet, J.M., Bion, J., Parker, M.M., Jaeschke, R., Reinhart, K., Angus, D.C., Brun-Buisson, C., Beale, R., Calandra, T., Dhainaut J-F, Gerlaan, H., Harvey, M., Marini, J.J., Marshall, J., Ranieri, M., Ramsay, G., Sevransky, J., Thompson, B.T., Townsend, S., Venoer, J.S., Zimmerman, J.L. and Vincent J-L. Surviving Sepsis Campaign:

International guidelines for management of severe sepsis and septic shock: 2008. *Critical Care Medicine*, 2008, vol 36, no 1, pp 296-327.

De Jonghe, B., Bastuji-Garin, S., Durand, M-C., Malissin, I., Rodrigues, P., Celf, C., Outini, H., and Sharshar, T. *Critical Care Medicine*, 2007, vol 35, pp 2007-2015.

De Wit, M., Miller, K.B., Green, D.A., Ostman, H-E., Gennings, C. and Epstein, S.K. Ineffective triggering predicts increased duration of mechanical ventilation. *Critical Care Medicine*, 2009, vol 37, no 10, pp 2740-2745.

De Jong, W, van Aarden, W.M.C, Kraan, J., Koëler, G.H. and Van der Schans, C.P. Inspiratory muscle training in patients with cystic fibrosis. *Respiratory Medicine*, 2001, vol 95, pp 31-36.

Díaz, M.C., Ospina-Tascón, G.A. and Salazar, B.C.C. Respiratory muscle dysfunction: A multicausal entity in the critically ill patient undergoing mechanical ventilation. *Archivos De Bronconeumologia*, 2014, vol 50, no 2, pp 73-77.

Dos Santos, C.C. and Batt, J. ICU-acquired weakness: Mechanisms of disability. *Current Opinion of Critical Care*, 2012, vol 18, pp 509-517.

Dowdy, D.W., Eid, M.P., Mendez-Tellez P.A., Pronovost, P.J., Herridge, M.S. and Needham, D.M. Quality of life in adult survivors of critical illness: A systematic review of the literature. *Intensive Care Medicine*, 2005, vol 31, pp 611-620.

Downey, A.E., Chenoweth, L.M., Townsend, D.K., Ranum J.D., Ferguson C.S. and Harms C.A. Effects of inspiratory muscle training on exercise responses in normoxia and hypoxia. *Respiratory Physiology and Neurobiology*, 2007, vol 156, pp 137-146.

Elliot, D., Denehy, L., Berney, S. and Alison, J.A. Assessing physical function and activity for survivors of a critical illness: A review of instruments. *Australian Critical Care*, 2011, vol 24, pp 155-166.

Elliott, D., McKinley, S., Alison, J., Aitken L.M., King, M., Leslie, G.D., Kenny, P., Taylor, P., Foley, R. and Burmeister, E. Health-related quality of life and physical recovery after a critical illness: a multi-centre randomised controlled trial of a home-based physical rehabilitation program. *Critical Care*, 2011, vol 15, no 3, pp 1-10.

Ely, E.W., Shintani, A., Truman, B., Speroff, T., Gordon, S.M., Harell Jnr, F.E.H., Inouye, S.K., Bernard, G.R. and Dittus, R.S. Delirium as a predictor of mortality in mechanically ventilated patients in the Intensive Care Unit. *Journal of the American Medical Association*, 2004, vol 291, pp 1753-1762.

Enright, S., Chatham, K., Lonescu, A.A., Unnithan, V.B. and Shale, D.J. Inspiratory muscle improves lung function and exercise capacity in adults with cystic fibrosis. *Chest*, 2004, vol 126, no 2, pp 405-411.

Evans, J.A., and Whitelaw, W.A. The assessment of maximal respiratory mouth pressures in adults. *Respiratory Care*, 2009, vol 54, no 10, pp 1348-1359.

Falk, D.J., DeRuisseau K.C., Van Gammeren, D.L., Deering, M.A., Kavazis, A.N. and Powers S.K. Mechanical ventilation promotes redox status alterations in the diaphragm. *Journal of Applied Physiology*, 2006, vol 101, pp 1017-1024.

Feng, Y., Amoateng-Adjepong, Y., Kaufman, D., Gheorghe, C. and Manthous, C.A. Age, duration of mechanical ventilation, and outcomes of patients who are critically ill. *Chest Journal*, 2009, vol 136, pp 759-764.

Fox, S.I. *Human Physiology*. 2004. Eighth Edition. United States, Lange, M.J (ed.).

Gayan-Ramirez, A. and Decramer, M. Effects of mechanical ventilation and diaphragm function and biology. *European Respiratory Journal*, 2002, vol 20, pp 1579-1586.

Geddes, E.L., O'Brien, K., Reid, W.D., Brooks, D. and Crowe, J. Inspiratory Muscle Training in patients with Obstructive Pulmonary Disease: An update of systemic review. *Respiratory Medicine*, 2008, vol 102, pp 1715-1729.

Ghadiali, S. and Nana-Sinkam, P. Lungs respond to hospital ventilator as if it were an infection. [Online]. Available at <http://researchnews.osu.edu/archive/lungvent.htm>. [Accessed 24/12/2014].

Gidani, H., Vyas, A. and Kar, A.K. A study of ventilator-associated pneumonia: Incidence, outcome, risk factors and measures to be taken for prevention. *Indian Journal of Anaesthesiology*, 2010, vol 54, no 6, pp 535-540.

Girard, T.D. and Bernard, G.R. Mechanical ventilation in ARDS: A state-of-the-art-review. *Chest*, 2007, vol 131, pp 921-929.

Goldstone, J. The Pulmonary physician in critical care, 10: Difficult weaning. *Thorax*, 2002, vol 57, pp 986-991.

Gosselink, R., Bott, J., Johnson, M., Dean, E., Nava, S., Norrenberg, M., Schönhofer, B., Stiller, K., Van der Leur, H., and Vincent, J.L. Physiotherapy for adult patients with critical illness: Recommendations of the European Respiratory Society of Intensive Care Medicine Task Force on Physiotherapy for Critically Ill Patients. *Intensive Care Medicine*, 2008, vol 34, pp 1188-1199.

Helliwell, T.R., Wilkinson, A., Griffiths, R.D., McClelland, Palmert, T.E.A. and Bone, J.M. Muscle fibre atrophy in critically ill patients is associated with the loss of myosin filaments and the presence of lysosomal enzymes and ubiquitin. *Neuropathology and Applied Neurobiology*, 1998, vol 24, pp 507-517.

Herridge, M.S., Cheung, A.M., Tansey, C.M., Matte-Martyn, A., Diaz-Granados, N., Al-Saidi, F., Cooper, A.B., Guest, C.B., Mazer, C.D., Mehta, S., Stewart, T.E., Barr, A., Cook, D. and Slutsky, A.S. One-year outcome in survivors of the acute respiratory distress syndrome. *New England Journal of Medicine*, 2003, vol 348, no 8, pp 683-693.

Herridge, M.S., Tansey, C.M., Matté, A., Tomlinson, G., Diaz-Granados, N., Cooper, A.B., Guest, C.B., Mazer, C.D., Mehta, S., Stewart, T.E., Kudlow, P., Cook, D. Slutsky, A.S. and Cheung, A.M. Functional disability 5 years after acute respiratory distress syndrome. *New England Journal of Medicine*, 2011, vol 368, no 14, pp 1293-1304.

Heyland, D.K., Dhaliwal, R., Drover, J.W., Gramlich, L. and Dodek, P. Canadian clinical practice guidelines for nutrition support in mechanically ventilated, critically ill adult patients. *Journal of Parental and Enteral Nutrition*, 2003, vol 27, pp 355-383.

Hill, K., Dennis, D.M. and Patman, S.M. Relationships between mortality, morbidity, and physical function in adults who survived a period of prolonged mechanical ventilation. *Journal of Critical Care*, 2013, vol 28, pp 427-432.

Hofhuis, J.G.M., Spronk, P.E., van Stel, H.F., Schrijvers, G.J.P., Rammes, J.H. and Bakker, J. The impact of critical illness on perceived health-related quality of Life during ICU treatment; hospital stay; and after hospital discharge: a long-term follow-up study. *Chest*, 2008, vol 133, pp 337-385.

Jubran, A. Critical illness and Mechanical Ventilation: Effects on the Diaphragm. *Respiratory Care*, 2006, vol 51, no 9, pp 1054-1064.

Karakurt, Z., Fanfulla, F., Cerianca, P., Carlucci, A., Aróssi, M., Colombo, R., Karkurt, S. and Nava, S. Physiologic determinants of prolonged mechanical ventilation in patients after major surgery. *Journal of Critical Care*, 2012, vol 27, pp 221.e9-221.e16.

Kelly, M.A. and McKinley, S. Patient recovery after critical illness at early follow-up. *Journal of Clinical Nursing*, 2010, vol 19, pp 691-700.

- Khalil, Y., Mustafa, E.E-D., Youssef, A., Imam, M.H. and Behiry, A.F.E. Neuromuscular dysfunction association with delayed weaning from mechanical ventilation in patients with respiratory failure. *Alexandria Journal of Medicine*, 2012, vol 48, pp 223-232.
- Khamiees M., Raju, P., DeGirolamo, A., Amoateng-Adjepong, Y. and Manthous, C.A. Predictors of extubation outcome in patients who have successfully completed a spontaneous breathing trial. *Chest*, 2000, vol 120, no 4, pp 1262-1270.
- Latronico, N. and Bolton C.F. Critical illness polyneuropathy and myopathy: A major cause of muscle weakness and paralysis. *Lancet Neurological*, 2011, vol 10, pp 931-941.
- Martin, A.D., Smith, B.K. and Gabrielli, A. Mechanical ventilation, diaphragm weakness and weaning: A rehabilitation perspective. *Respiratory Physiology and Neurobiology*, 2013, vol 189, pp 377-383.
- Martin-Loeches, I., de Haro, C., Dellinger, R.P., Ferer, R., Phillips, G.S., Levy, M.M. and Artigas, A. Effectiveness of an inspiratory pressure limited approach to mechanical ventilation in septic patients. *European Respiratory Journal*, 2013, vol 41, pp 157-164.
- McConnell, A.K. and Griffiths, L.A. Acute Cardiopulmonary Responses to Inspiratory Pressure Threshold Loading. *Sport Exercise*, 2010, vol 42, no 9, pp 1696-1703.
- McConnell, A.K. *Respiratory Muscle Training (Theory and Practice)*, 2013, Chapter 2-7, pp 57-96.
- Menon, N., Joffe, A. M., Deem, S., Yanez, N.D., Grabinsky, A., Dagal, H.C.D., Daniel, S. and Treggiari, M.M. Occurrence and complications of tracheal reintubation in critically ill adults. *Respiratory Care*, 2012, vol 57, no 10, pp 1555-1563.
- Meeusen, R., Duclos, M., Gleeson, M., Rietjens, G., Steinacker, J. and Urhausen, A. Prevention, diagnosis and treatment of the overtraining syndrome. *European Journal of Sport Science*, 2006, vol 6, no 1, pp 1-14.
- Moodie, L., Reeves, J. and Elkins, M. Inspiratory muscle training increases inspiratory muscle strength in patients weaning from mechanical ventilation: A systematical review. *Journal of Physiotherapy*, 2011, vol 57, pp 213-221.
- National Institute for Health and Care Excellence (UK). 2009. Rehabilitation after critical illness. *NICE Clinical Guidelines* no 3. [Online]. Available at <http://www.ncbi.nlm.nih.gov/books/NBK11653>. [Accessed 11 September 2014].
- Nava, S. Rehabilitation of patients admitted to a respiratory intensive care unit. *Archives of Physical Medicine and Rehabilitation*, 2009, vol 79, pp 849-854.
- Naved, S.A., Siddiqui, S. and Khan, F.H. APACHE-II score correlation with mortality and length of stay in an intensive care unit. *Journal of the College of Physicians and Surgeons Pakistan*, 2011, vol 21, no 1, pp 1-8.
- Nemer, S.N., Barbas, C.S.V., Caldeira, J.B., Guimarães, B., Azeredo, L.M., Gago, R. and Souza, P.C.P. Evaluation of Maximal inspiratory pressure, tracheal airway occlusion pressure and its ration in the weaning outcome. *Journal of Critical Care*, 2009, vol 24, pp 441-445.
- Nicholls, D. 'Breathlessness: A qualitative model of meaning'. *Physiotherapy*, 2000, vol 86, no 1, pp 23-27.
- Nordon-Craft, A., Schenkman, M., Ridgeway, K., Benson, A. and Moss, M. Physical Therapy Management and Patient outcomes following ICU-Acquired weaknes: A Care series. *Journal of neurologic Physical Therapy*, 2011, vol 35, pp 133-140.
- Loss, S.H., Marchese, C.B., Bonniati, M.M., Wawrzeński, I.C., Oliveira, R.P., Nunes, L.N. and Victorino, J.A. Prediction of chronic illness in a general intensive care unit. *Revista da Associação Médica Brasileira*, 2013, vol 59, no 3, pp 241-247.

- Orford, N., Cattigan, C., Brennan, S.L., Kotowicz, M., Pasco, J. and Cooper, D.J. The association between critical illness and changes in bone turnover in adults: a systematic review. *Osteoporosis International*, 2014, vol 25, no 10, pp 2335-2346.
- Patsaki, I., Papadopoulos, E., Sidiras, G., Christakou, A., Kouvarakos, A. and Markaki, V. The effectiveness of inspiratory muscle training in weaning critically ill patients from mechanical ventilation. *Hospital Chronicles*, 2013, vol 8, no 2, pp 86-90.
- Petrof, B.J., Jaber, S. and Matecki, S. Ventilator-induced diaphragmatic dysfunction. *Critical Care*, 2010, vol 16, pp 19-25.
- Petrovic, M., Lahrmann, H., Pohl, W. and Wonke, T. Idiopathic diaphragmatic paralysis-Satisfactory improvement of inspiratory muscle function by inspiratory muscle training. *Respiratory Physiology and Neurobiology*, 2006, vol 165, pp 266-267.
- Plani, N., Becker, P. and Van Aswegen, H. The use of a weaning and extubation protocol to facilitate effective weaning and extubation from mechanical ventilation in patients suffering from traumatic injuries: A non-randomized experimental trial comparing a prospective to retrospective cohort. *Physiotherapy Theory and Practice*, 2013, vol 29, no 3, pp 211-221.
- Powers, S.K., Kavazis, A.N. and Levine, S. Prolonged mechanical ventilation alters diaphragmatic structure and function. *Critical Care Medicine*, 2009, vol 37, pp 347-353.
- Prakash, P., Krishna, K. and Bhatia, D. Usefulness of SAPS II scoring system as an early predictor of outcome in ICU Patients. *Journal Indian Academy of Clinical Medicine*, 2006, vol 7, no 3, pp 201-205.
- Prentice, C.E., Paratz, J.D. and Bersten, A.D. Differences in the degree of respiratory and peripheral muscle impairment are evident on clinical, electrophysiological and biopsy testing in critically ill adults: a qualitative systematic review. *Critical Care and Resuscitation*, 2010, vol 12, no 2, pp 111-120.
- Puthucherry, Z., Harridge, S. and Hart, N. Skeletal muscle dysfunction in critical care; wasting, weakness and rehabilitation strategies. *Critical Care Medicine*, 2010, vol 38, no 10, pp 676-682.
- Puthucherry, Z., Montgomery, H., Moxham, J., Harridge, S. and Hart, N. Structure to function: muscle failure in critically ill patients. *Journal Compilation: The Physiological Society*, 2010, vol 588, no 23, pp 4641-4648.
- Puthucherry, Z.A., Rawal, J., McPhail, M., Connolly, B., Ratnayake, G., Chan, P., Hopkinson, N.S., Padhke, R., Dew, T., Sidhu, P.S., Velloso, C., Seymour, J., Agle, C.C., Selby, A., Limb, M., Edwards, L.M., Smith, K., Rowleson, A., Rennie, M.J., Moxham, J., Harridge, S.D.R., Hart, N. and Montgomery H.E. Acute Skeletal Muscle Wasting in Critical Illness. *Journal of American Medical Association*, 2013, vol 310, no 15, pp 1591-1600.
- Rahman, I. and McNee, W. Oxidative stress and regulation of glutathione in lung inflammation. *European Respiratory Journal*, vol 16, no 3, pp 534-554.
- Ratnovsky, A., Elad, D. and Halpern, P. Mechanics of respiratory muscles. *Respiratory Physiology and Neurobiology*, 2008, vol 163, pp 82-89.
- Rattray, J.E. and Hull, A.M. Emotional outcome after intensive care: literature review. *Journal of Advanced Nursing*, 2007, vol 64, no 1, pp 2-13.
- Respironics Healthscan Asthma and Allergy Products. *Threshold IMT*, 2000. Reference, HS730EU.
- Reid, C.L., Campbell, I.T. and Little, R.A. Muscle wasting and energy balance in critical illness. *Clinical Nutrition*, 2004, vol 23, pp 273-280.

Riera, H.S., Rubio, T.M., Ruiz, F.O., Ramos, P.C., Oters, D.D.C., Elias, H. and Gomez, J.Z. Inspiratory muscle training in patients with COPD. Effect on dyspnoea, exercise performance and quality of life. *Chest*, 2001, vol 120, pp 748-756.

Rodriguez, P.O., Settan, M., Maskin, L.P., Bonelli, I., Vidomlansky, S.R., Attie, S., Frosiani, S.L., Kozima, S. and Valentini, R. Muscle weakness in septic patients requiring mechanical ventilation: Protective effect of transcutaneous neuromuscular electrical stimulation. *Journal of Critical Care*, 2012, vol 27, pp 319. e1-319.e8.

Romer, L.M. and McConnell, A.K. Specificity and Reversibility of Inspiratory Muscle Training. *Medicine and Science in Sports and Exercise*, 2003, vol 35, no 2, pp 237- 244.

Sandham, J. Fundamentals of Ventilation, 2005. [Online]. Available on <http://www.ebme.co.uk/articles/clinical-engineering/37-fundamentals-of-ventilation>. [Accessed 24 December 2014].

Seeley, E.J. Updates in the Management of the Acute Lung Injury: A focus on the overlap Between AKI and ARDS. *Advances in Chronic Kidney Disease*, 2013, vol 20, no 1, pp 14-20.

Seymour, C.W., Martinez, A., Christie, J.D. and Fuchs, B.D. The outcome of extubation failure in a community hospital intensive care unit: a cohort study. *Critical Care*, 2004, vol 10, pp 322-327.

Shah, P.B. Intention-to-treat and per-protocol analysis. *Canadian Medical Association Journal*, 2011, vol 183, no 6, pp 696.

Shoemaker, M.J., Curtis, A.M., Vangsnes, E. and Dickinson, M.G. Clinically meaningful change estimates for the six-minute walk test and daily activity in individuals with chronic heart failure. *Cardiopulmonary Physical Therapy Journal*, 2013, vol 24, no 3, pp 21-19.

Shoemaker, M.J., Donker, S. and LaPoe, A. Inspiratory muscle training in patients with chronic obstructive pulmonary disease: The state of the Evidence. *Cardiopulmonary Physical Therapy Journal*, 2009, vol 20, no 3, pp 5-15.

Shosbree, J., Campbell, L.J., Ibrahim, F., Hopkins, P., Vizcaychipi, M., Straanan, S. and Post, F.A. Late HIV diagnosis is a major risk factor for intensive care unit admission in HIV-positive patients: a single centre observational cohort study. *BMC, Infectious Diseases*, 2013, vol 13, no 23, pp 1471-2334.

Skinner, E.H., Berney, S., Worillow, S. and Denery, L., Rehabilitation and Exercise prescription in Australian intensive care units. *Physiotherapy*, 2008, vol 94, pp 220-229.

Slutsky, A.S., Parsons, P.E. and Finlay, G. Inflammatory mechanisms of lung injury during mechanical ventilation [Online]. Available at <http://www.uptodate.com/contents/inflammatory-mechanisms-of-lung-injury-during-mechanical-ventilation#H1>. [Accessed 24 December 2014].

Soni, N. and Williams, P. Positive pressure ventilation: what is the real cost? *British Journal of Anaesthesia*, 2008, vol 101, no 4, pp 446-457.

Stein, R., Maia, C.P., Silveira, A.D., Chiappa, G.R., Myers, J. and Ribeiro, J.P. Inspiratory Muscle Strength as a Determinant of Functional Capacity Early After Coronary Artery Bypass Graft Surgery. *Archives of Physical Medicine and Rehabilitation*, 2009, vol 90, pp 1685-1691.

Stiller, K. Physiotherapy in intensive care: an updated systematic review. *Chest*, 2013, vol 144, no 3, pp 825-847.

Stricker, K.H., Sailer, S., Uehlinger, D.E., Rothen, H.U., Zuercher Zenklusen, R.M. and Frick, S. Quality of life 9 years after an intensive care unit stay: A long-term outcome study. *Journal of Critical Care*, 2011, vol 26, pp 379-387.

Su, W-L., Chen Y-H., Chen, C-W., Yang, S-H., Su, C-H., Perng, W-H., Wu, C-H. and Chen, J-H. Involuntary cough strength and extubation outcomes for patients in an ICU. *Chest*, 2010, vol 137, pp 777-782.

Sun, Z-T., Yang, C-Y., Miao, L.J., Zhang, S-F., Han, X-P., Ren, S-E., Sun, X-Q. and Cao, Y-N. Effects of mechanical ventilation with different tidal volume on oxidative stress and antioxidant in lung. *Journal of Anesthesia*, 2014, 1438-8359.

Thille, A.W., Richard, J-M.M. and Brochard, L. The decision to extubate in the intensive care unit. *American Journal and Respiratory Critical Care Medicine*, vol 187, no 12, pp 1294-1302.

Thomas, A.J. Systematic Review: Physiotherapy led early rehabilitation of the patient with critical illness. *Physical Therapy Reviews*, 2011, vol 16, no 1, pp 46-57.

Thomas, J.R. and Von Gunten, C.F. Clinical management of dyspnoea, *Lancet Oncology*, 2002, vol 3, pp 223-228.

Toussirot, É. Predictive factors for disability as evaluated by the health assessment questionnaire in rheumatoid arthritis: A literature review. *Inflammation and Allergy-Drug Targets*, 2010, vol 9, pp 51-59.

Tupchong K., Koyfman, A. and Foron, M. Sepsis; severe sepsis and septic shock: A review of literature. *African Journal of Emergency Medicine*, 2014, no.193.

Turner, L.A., Mickleborough, T.D., McConnell, A.K., Stager, J.M., Tecklenburg-Lund, S. and Lindley, M.R. Effect of Inspiratory Muscle Training on Exercise Tolerance in Asthmatic Individuals. *Medicine and Science in Sports and Exercise*, 2011, vol 43, no 11, pp 2031-2038.

Vadász, I., Weiss, C.H. and Sznajder, J.I. Ubiquitination and Proteolysis in Acute Lung Injury. *Chest*, 2012, vol 141, no 3, pp 763-771.

Van Aswegen, H., Richards, G.A., Goosen, J. and Bekker, J. The effect of penetrating trunk trauma and mechanical ventilation on the recovery of adult survivors after hospital discharge. *South African Journal of Critical Care*, 2010, vol 26, no 1, pp 25-32.

Vincent, B., Timsit, J-F., Auburtin, M., Schortgen, F., Bouodma, L., Wolff, M. and Regnier, B. Characteristics and outcomes of HIV-infected patients in the ICU: impact of the highly active antiretroviral treatment era. *Intensive Care Medicine*, 2004, vol 30, pp 859-866.

Van Aswegen, H., Myezwa, H., Mudzi, W., and Becker, P. Health-related quality of life of survivors of penetrating trunk trauma in Johannesburg, South Africa. *European Journal of Trauma and Emergency surgery*, 2011, vol 37, pp 419-426.

Volpe, M.S., Adams, A.B., Amato, M.B.P. and Marini, J.J. Ventilation patterns influence airway secretion movement. *Respiratory Care*, 2008, vol 53, no 10, pp 1287-1294.

Winkelman, C. Bed rest in health and critical illness. *Advanced Critical Care*, 2009, vol 20, no 3, pp 254-266.

Winkelman, C., Higgins, P.A., Chen, Y.J.K and Levine, A.D. Cytokines in Chronically Critically Ill Patients after Activity and Rest. *Biological Research of Nursing*, 2007, vol 8, pp 261-271.

Yang, K.L. and Tobin, M.J. A Prospective Study of Indexes Predicting the Outcome of Weaning From Mechanical Ventilation. *The New England Journal of Medicine*, 1991, vol 324, no 21, pp 1446-1450.

APPENDIX 1

▪ ETHICAL CLEARANCE CERTIFICATE



UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG
Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Ms NV Thupana

CLEARANCE CERTIFICATE

M120473

PROJECT

Use of the Inspiratory Muscle Trainer Device
after Extubation in a Critical Care Setting

INVESTIGATORS

Ms NV Thupana.

DEPARTMENT

Department of Physiotherapy

DATE CONSIDERED

04/05/2012

DECISION OF THE COMMITTEE*

Approved unconditionally

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 03/07/2012

CHAIRPERSON


(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable
cc: Supervisor : Dr H van Aswegen

DECLARATION OF INVESTIGATOR(S)

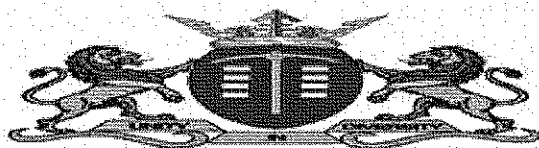
To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10004, 10th Floor, Senate House, University.

I/we fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. I agree to a completion of a yearly progress report.

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES...

APPENDIX 2

▪ CMJAH LETTER OF PERMISSION



**health and
social development**
Department: Health and Social Development
GAUTENG PROVINCE

CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL

Academic

Enquiries:
Office of the Chief Executive Officer
Charlotte Maxeke Johannesburg

Tell: 011 488 3792

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lindiwe.mngomezulu@gauteng.gov.za

Date: 5 April 2012

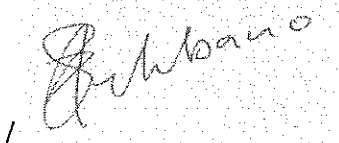
Attention Ms.N Thupana
Charlotte Maxeke Academic Johannesburg Hospital

Dear Ms. Thupana

RE: "The use of the inspiratory muscle trainer device in critical care setting after extubation."

Please note that your above request is provisionally approved. Your study can only commence once ethics approval is obtained.

Yours sincerely

A handwritten signature in cursive script, appearing to read 'Barney Selebano'.

Dr. Barney Selebano
Chief Executive Officer

APPENDIX 3

▪ SOUTH AFRICAN NATIONAL TRIAL REGISTRY CERTIFICATE CONFIRMATION

SOUTH AFRICAN NATIONAL CLINICAL TRIALS REGISTRY CERTIFICATE (DOH-27-0614-4750)

National Ethics Application #: 3750

confirmation@sanrr.co.za

Mon 2014/06/09 04:59 PM

Dear Prof Heleen van Aswegen

Your Application, "Use of inspiratory muscle training after extubation." Protocol # "00140184911055121105RM" has been assigned the following unique DOH Trial Number: "DOH-27-0614-4750".

Kind regards,

Department of Health

APPENDIX 4

▪ TEMPORARY CONSENT SHEET

TEMPORARY CONSENT

- I hereby confirm that I have been informed by the researcher, Nthabiseng Thupana about the nature, conduct, benefits and risks of the study:
- Use of the Inspiratory Muscle Trainer (IMT) device after extubation in a Critical Care Setting.
- I have also received, read and understood the above written information (Participant Information sheet and Informed consent) regarding the study.
- I am aware that the results of the study. Including personal details regarding my sex, age, date of birth, initials and diagnosis will be anonymously processed into a research paper.
- I may, at any stage, without prejudice, withdraw my consent and participation in the study.

PARTICIPANT:

Printed Name	Signature/ Mark/ Thumbprint	Date and Time

I, Nthabiseng Thupana, herewith confirm that the above participant has been fully informed about the nature, conduct and risks of the above study.

RESEARCHER:

Printed Name	Signature	Date and Time

APPENDIX 5

▪ INFORMATION DOCUMENT

INFORMATION DOCUMENT

Use of the Inspiratory Muscle Trainer (IMT) device after extubation in a Critical Care Setting

Hello, my name is Nthabiseng Thupana and I am a current postgraduate student at the University of Witwatersrand.

You are invited to participate in this research study. Your participation in this study is entirely voluntary. Before agreeing to participate, it is important that you understand what is involved before you agree to take part in this study. If you have any questions or concerns regarding this study, please do not hesitate to ask me. You are not obliged to participate in this study, you should not agree to take part unless you understand and are satisfied with the procedures involved. If you decide to take part in this study, you will be asked to sign this document to confirm that you understand the study.

Purpose of the study:

The purpose of this study is to investigate the effect of using the IMT device after extubation after prolonged mechanical ventilation.

Study details:

The study will be conducted at the Charlotte Maxeke Academic Johannesburg Hospital (ICU and wards). A total of one hundred participants will be recruited for this study. The participants will be requested to fill out three questionnaires; the researcher will perform tests such as blood pressure, heart rate, saturation, maximal inspiratory and expiratory pressure. Initially the tests, treatments and questionnaires will be done in the ICU but when the patient is transferred to the wards we will proceed in the respective wards till the patient is discharged. Estimated time to complete questionnaires: 15 minutes, tests will take approximately 20 minutes, treatment: 30 min, IMT: 10-30 min. On the day of discharge, one and three months after discharge the researcher will perform the tests including the six minute walk test (after this test the participant will complete one questionnaire) and participants will be requested to complete the questionnaires. After discharge; patients will be come back after one and three months for follow up tests in the physiotherapy department (258-yellow block).

Risks:

Participants may find some procedures tiring and some may experience dizziness and nausea initially.

Benefits:

Improvement in the overall physical wellbeing with increased inspiratory muscle strength and endurance.

RIGHTS AS A PARTICIPANT IN THIS STUDY:

Voluntary participation: the participants/ patients are not obliged to commit to this study; the patient may decline participation or withdraw from the study at anytime without stating a reason.

Withdrawal: Your withdrawal from this study will not affect your access to other medical/ physiotherapy care.

Confidentiality/ Privacy: Patients/participants' personal information including research data and hospital records will be kept strictly confidential.

Reimbursement for the study participation: You will not be paid to participate in this study but your transport will be reimbursed adequately.

Ethical approval: This study protocol has been submitted to the University of the Witwatersrand, Human Research Ethics Committee (HREC) and written approval has been granted by that committee. My contact details (available 24hrs): Nthabiseng Thupana: 0824701406

If further information regarding your rights as a research participant, or complaints regarding this research study, you may contact Prof. P. Cleaton Jones, Chairperson of the University of the Witwatersrand, Human Research Ethics Committee (HREC), which is an independent committee, established to help protect the rights of research participants at (011) 717 1234

Signed**Date**

APPENDIX 6

▪ INFORMED CONSENT

INFORMED CONSENT

I hereby confirm that I have been informed by the researcher, Nthabiseng Thupana about the nature, conduct, benefits and risks of the study:

- Use of the Inspiratory Muscle Trainer (IMT) device after extubation in a Critical Care Setting.
- I have also received, read and understood the above written information (Participant Information sheet and Informed consent) regarding the study.
- I am aware that the results of the study. Including personal details regarding my sex, age, date of birth, initials and diagnosis will be anonymously processed into a research paper.
- I may, at any stage, without prejudice, withdraw my consent and participation in the study.

PARTICIPANT:

Printed Name	Signature/ Mark/ Thumprint	Date and Time

I, Nthabiseng Thupana, herewith confirm that the above participant has been fully informed about the nature, conduct and risks of the above study.

RESEARCHER:

Printed Name	Signature	Date and Time

APPENDIX 7

▪ MODIFIED BORG SCALE

MODIFIED BORG DYSPNOEA SCALE

0	Nothing at all
0.5	Very, very slight (just noticeable)
1	Very slight
2	Slight
3	Moderate
4	Somewhat severe
5	Severe
6	
7	Very severe
8	
9	Very, very severe (almost maximal)
10	Maximal

APPENDIX 8

▪ EQ-5D

Figure 1: EQ-5D (UK English version)

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

- I have no problems in walking about ☐
- I have some problems in walking about ☐
- I am confined to bed ☐

Self-Care

- I have no problems with self-care ☐
- I have some problems washing or dressing myself ☐
- I am unable to wash or dress myself ☐

Usual Activities (e.g. work, study, housework, family or leisure activities)

- I have no problems with performing my usual activities ☐
- I have some problems with performing my usual activities ☐
- I am unable to perform my usual activities ☐

Pain/Discomfort

- I have no pain or discomfort ☐
- I have moderate pain or discomfort ☐
- I have extreme pain or discomfort ☐

Anxiety/Depression

- I am not anxious or depressed ☐
- I am moderately anxious or depressed ☐
- I am extremely anxious or depressed ☐

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

**Your own
health state
today**

Best
imaginable
health state

100

90

80

70

60

50

40

30

20

10

0

Worst
imaginable
health state

APPENDIX 9

STANFORD UNIVERSITY HAQ

HEALTH ASSESSMENT QUESTIONNAIRE® Stanford University School of Medicine Division of Immunology & Rheumatology

Participant number _____

Date _____

In this section we are interested in learning how your illness affects your ability to function in daily life. Please feel free to add any comments on the back of this page.

Please check the response which best describes your usual abilities OVER THE PAST WEEK:

	Without ANY difficulty ⁰	With SOME difficulty ¹	With MUCH difficulty ²	UNABLE to do ³
DRESSING & GROOMING				
Are you able to:				
-Dress yourself, including tying shoelaces and doing buttons?	☐	☐	☐	☐
-Shampoo your hair?	☐	☐	☐	☐
ARISING				
Are you able to:				
-Stand up from a straight chair?	☐	☐	☐	☐
-Get in and out of bed?	☐	☐	☐	☐
EATING				
Are you able to:				
-Cut your meat?	☐	☐	☐	☐
-Lift a full cup or glass to your mouth?	☐	☐	☐	☐
-Open a new milk carton?	☐	☐	☐	☐
WALKING				
Are you able to:				
-Walk outdoors on flat ground?	☐	☐	☐	☐
-Climb up five steps?	☐	☐	☐	☐

Please check any AIDS OR DEVICES that you usually use for any of these activities:

- | | |
|-------------------------------------|---|
| ☐ Cane | ☐ Devices used for dressing (button hook, zipper pull, long-handled shoe horn, etc.) |
| ☐ Walker | ☐ Built up or special utensils |
| ☐ Crutches | ☐ Special or built up chair |
| ☐ Wheelchair | ☐ Other (Specify: _____) |

Please check the response which best describes your usual abilities **OVER THE PAST WEEK**:

	Without ANY difficulty ⁰	With SOME difficulty ¹	With MUCH difficulty ²	UNABLE to do ³
HYGIENE				
Are you able to:				
-Wash and dry your body?	☐	☐	☐	☐
-Take a tub bath?	☐	☐	☐	☐
-Get on and off the toilet?	☐	☐	☐	☐
REACH				
Are you able to:				
-Reach and get down a 5-pound object (such as a bag of sugar) from just above your head?	☐	☐	☐	☐
-Bend down to pick up clothing from the floor?	☐	☐	☐	☐
GRIP				
Are you able to:				
-Open car doors?	☐	☐	☐	☐
-Open jars which have been previously opened?	☐	☐	☐	☐
-Turn faucets on and off?	☐	☐	☐	☐
ACTIVITIES				
Are you able to:				
-Run errands and shop?	☐	☐	☐	☐
-Get in and out of a car?	☐	☐	☐	☐
-Do chores such as vacuuming or yardwork	☐	☐	☐	☐

Please check any **AIDS OR DEVICES** that you usually use for any of these activities:

- | | |
|--|--|
| ☐ Raised toilet seat | ☐ Bathtub bar |
| ☐ Bathtub seat | ☐ Long-handled appliances for reach |
| ☐ Jar opener (for jars previously opened) | ☐ Long-handled appliances in bathroom |
| | ☐ Other (Specify: _____) |

APPENDIX 10

▪ SAPS II SHEET

Simplified Acute Physiology Score (SAPS II) Calculator

Note: Use the worst value for each physiological variable within the past 24 hours.

Age		years
Heart rate		bpm ①
Systolic BP		mmHg
Temp		C or F ②
Mechanical ventilation or CPAP	☒ Yes ☐ No	③
PaO ₂		mmHg
FIO ₂		%
Urine output		mL
	per hour	
BUN		mg/dL
WBC		x 10 ⁹ /L
Potassium		mEq/L
Sodium		mEq/L
Bicarbonate		mEq/L
Bilirubin		mg/dL
Glasgow coma score		④
Chronic diseases	☐ Metastatic cancer ① ☐ Hematologic malignancy ③ ☐ AIDS ②	
Type of admission	Scheduled surgical	⑤
	Reset Calculate	

APPENDIX 11

APACHE II SHEET

Calculates the APACHE-II score to estimate predicted mortality.

Does the patient have a history of chronic organ insufficiency or immunocompromise?

- ☐ Yes, and is s/p emergency surgery.
☐ Yes, but is not s/p operation.
☐ Yes, and is s/p elective surgery.
☐ No.

Does the patient have acute renal failure?

☐ Yes

Age

years old

Temperature (Rectal, Celsius)

°C or °F (yes, either!)

Mean Arterial Pressure (MAP)

pH (Arterial)

Heart Rate

bpm

Respiratory Rate (either ventilated or spontaneous)

bpm

Sodium (Serum)

mEq/L

Potassium (Serum)

mEq/L

Creatinine (Serum)

mg/dL

Hematocrit

White Blood Cell Count

$\times 10^3$ cells/mm³

Glasgow Coma Score

points

A-a Gradient (if FiO₂ ≥ 0.5)

mm Hg

PaO₂ (if FiO₂ < 0.5)

mm Hg

Click!

APPENDIX 12

▪ DATA COLLECTION SHEETS

PERSONAL INFORMATION

Patient number :
 Age :
 Gender :
 Date of admission :
 SAPS 2 score :
 Smoker : Yes ☐ No ☐

If yes, how many pack years:

Length of stay (LOS):

Number of days on mechanical ventilation:

Date of extubation :

Date of assessment (day 1 after extubation):

A. AFTER EXTUBATION

Data collected from Questionnaires:

EQ-5D:

▪ Comments:

HAQ:

▪ Comments:

Baseline Measurements:

Baseline measurements	Day 1 after extubation	Comments
HR		
SO2		
BP		
PiMax		
PeMax		

B. ON DISCHARGE**Data collected from Questionnaires:****EQ-5D:**

- Comments:

HAQ:

- Comments:

Baseline Measurements:

Baseline measurements	Day of discharge	After 6MWD	Comments
HR			
SO2			
BP			
PiMax			
PeMax			

6MWT:

Modified Borg Scale	
Oxygen therapy	
Walking aid	
Rests and stops	
Distance walked	
Time	
Modified Borg Scale	

Re-intubation rate and dates:**C. ONE MONTH AFTER DISCHARGE****EQ-5D:**

- Comments:

HAQ:

- Comments:

Baseline Measurements:

Baseline measurements	One month after discharge	After 6MWD	Comments
HR			
SO ₂			
BP			
PiMax			
PeMax			

6MWT:

Modified Borg Scale	
Oxygen therapy	
Walking aid	
Rests and stops	
Distance walked	
Time	
Modified Borg Scale	

D. THREE MONTHS AFTER DISCHARGE**Data collected from Questionnaires:****EQ-5D:**

- Comments:

HAQ:

- Comments:

Baseline Measurements:

Baseline measurements	Three months after discharge	After 6MWD	Comments
HR			
SO ₂			
BP			
PiMax			
PeMax			

6MWT:

Modified Borg Scale	
Oxygen therapy	
Walking aid	
Rests and stops	
Distance walked	
Time	
Modified Borg Scale	

APPENDIX 13

▪ PROGRESS NOTES

Patient number :

PiMax :

30% of PiMax :

(Please document detailed SOAP notes, including the distance walked during each treatment)

Date:	Date:
Date:	Date:

APPENDIX 14

▪ PHYSIOTHERAPY TREATMENT GUIDELINE

- Aerobic training and muscle strengthening: Upper limb and lower limb exercises:

Exercise intensity: determined by achieving a heart rate that is within 60-80% of age predicted maximum heart rate.

Training will start at five minutes of the intensity calculated, progression will be according to the patient's ability.

- Upper limb: ROM exercises(active/active-assisted), low resistance training with the use of water bottles (with various quantities of water to progress muscle training)
- Progression (level of water): $\frac{1}{4}$, $\frac{1}{2}$, $\frac{3}{4}$ and full.
Repetition: 3 sets of 12 repetitions.
- Lower limbs: ROM exercises (active/active-assisted), gluts strengthening: bridging, quadriceps strengthening: sit to stand, progressed to squat against the wall.
Repetition: 3 sets of 12 repetitions.
- Mobilisation of patients, with or without aid and with/ without oxygen (if unable to take steps, march on the spot for example will be acceptable), daily distance walked will be recorded.
- Respiratory system: manual chest physiotherapy, ACBT and FET

APPENDIX 15

▪ IMT TRAINING PROGRAMME

- Intensity will be derived from 30% of P_iMax.
- The patient is to sit in a comfortable position and a SpO₂ monitor will be attached to the patients' finger.
- Patient is advised to exhale as much as possible, "pinch their nose and seal their lips around the mouthpiece"
- The patient is requested to inspire/inhale enough to create enough pressure to keep the valve open "for a minimum of one second".
- Patients will take 4 sets of 6 breaths.
- Treatment will commence at ten minutes per session, progressed to fifteen, twenty and thirty minutes per session.
- Reassessment will occur when the patients can maintain 30 minutes of IMT training, then intensity will be increased to 40% or 50% of P_iMax.
- The patient will continue this treatment under the supervision of the research assistant once a day for five days of the week. The patient will be advised to continue with the IMT training twice more on their own before lunch and dinner.
- Safety/Precautions: chest pain, dizziness and SpO₂ below 90%

APPENDIX 16

▪ RESEARCH AND APPOINTMENT INFORMATION

Dear _____

Thank you for participating in this study. Please take the time to go through the information document again. The appointment dates are written on the next page.

Use of the Inspiratory Muscle Trainer (IMT) device after extubation in a Critical Care Setting. Hello, my name is Nthabiseng Thupana and I am a current postgraduate student at the University of Witwatersrand.

You are invited to participate in this research study. Your participation in this study is entirely voluntary. Before agreeing to participate, it is important that you understand what is involved before you agree to take part in this study. If you have any questions or concerns regarding this study, please do not hesitate to ask me. You are not obliged to participate in this study, you should not agree to take part unless you understand and are satisfied with the procedures involved. If you decide to take part in this study, you will be asked to sign this document to confirm that you understand the study.

Purpose of the study:

The purpose of this study is to investigate the effect of using the IMT device after extubation after prolonged mechanical ventilation.

Study details:

The study will be conducted at the Charlotte Maxeke Academic Johannesburg Hospital (ICU and wards). A total of one hundred participants will be recruited for this study. The participants will be requested to fill out three questionnaires; the researcher will perform tests such as blood pressure, heart rate, saturation, maximal inspiratory and expiratory pressure. Initially the tests, treatments and questionnaires will be done in the ICU but when the patient is transferred to the wards we will proceed in the respective wards till the patient is discharged. Estimated time to complete questionnaires: 15 minutes, tests will take approximately 20 minutes, treatment: 30 min, IMT: 10-30 min. On the day of discharge, one and three months after discharge the researcher will perform the tests including the six minute walk test (after this test the participant will complete one questionnaire) and participants will be requested to complete the questionnaires. After discharge; patients will be come back after one and three months for follow up tests in the physiotherapy department (258-yellow block).

Risks:

Participants may find some procedures tiring and some may experience dizziness and nausea initially.

Benefits:

Improvement in the overall physical wellbeing with increased inspiratory muscle strength and endurance.

RIGHTS AS A PARTICIPANT IN THIS STUDY:

Voluntary participation: the participants/ patients are not obliged to commit to this study; the patient may decline participation or withdraw from the study at any time without stating a reason.

Withdrawal: Your withdrawal from this study will not affect your access to other medical/ physiotherapy care.

Confidentiality/ Privacy: Patients/participants' personal information including research data and hospital records will be kept strictly confidential.

Reimbursement for the study participation: You will not be paid to participate in this study but your transport will be reimbursed adequately.

Ethical approval: This study protocol has been submitted to the University of the Witwatersrand, Human Research Ethics Committee (HREC) and written approval has been granted by that committee. My contact details (available 24hrs): Nthabiseng Thupana: 0824701406

If further information regarding your rights as a research participant, or complaints regarding this research study, you may contact Prof. P. Cleaton Jones, Chairperson of the University of the Witwatersrand, Human Research Ethics Committee (HREC), which is an independent committee, established to help protect the rights of research participants at (011) 717 1234

Appointment dates:

One month after hospital discharge: _____

Three months after hospital discharge: _____

Please meet me in Area 258 (yellow block); Physiotherapy Department. Please ask for Nthabiseng.

Thank you!

APPENDIX17

▪ TURNITIN ORIGINALITY REPORT



Turnitin Originality Report

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From Research Reports

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Marks, Guy B, Ezz, Wafaa Aust, Nathan To. "Respiratory health effects of exposure to low-NO₂ sub-µl unflued gas heaters in the classroom: a dou". Environmental Health Perspectives. Oct 2010 Issue
-
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118	< 1% match (publications) "PS 0849-1170". <i>Intensive Care Medicine</i> . 09/2006
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123	< 1% match (publications) Alfred Sciuto. "The Temporal Profile of Cytokines in the Bronchoalveolar Lavage Fluid in Mice Exposed to the Industrial Gas Phosgene". <i>Inhalation Toxicology</i> . 6/2003
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134	< 1% match (Internet from 07-Apr-2014) http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3929838/
135	< 1% match (Internet from 30-May-2009) http://content.onlinejacc.org/cgi/content/full/51/17/1663
136	< 1% match (publications) Bosnak-Gudu, M., "Effects of inspiratory muscle training in patients with heart failure", Respiratory Medicine, 201111
137	< 1% match (publications) Silva, Ivanizia S, Guilherme AF Fregonezi, Fernando AL Dias, Cibele TD Ribeiro, Ricardo O Guerra, Gardenia MH Ferreira, and Gardenia MH Ferreira, "Inspiratory muscle training for asthma", Cochrane Database of Systematic Reviews Reviews, 2013.
138	< 1% match (publications) Louise A. Turner, "Effect of Inspiratory Muscle Training on Exercise Tolerance in Asthmatic Individuals .", Medicine & Science in Sports & Exercise, 04/2011
139	< 1% match (publications) John A Griffiths, "Study protocol: The Intensive Care Outcome Network ('ICON') study", BMC Health Services Research, 2008
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141	< 1% match (publications) Lev-Tzion, Raffi, Anne Marie Griffiths, Oren Leder, Dan Turner, and Raffi Lev-Tzion, "Omega 3 fatty acids (fish oil) for maintenance of remission in Crohn's disease", Cochrane Database of Systematic Reviews, 2014.
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161	< 1% match (Internet from 30-Aug-2014) http://jama.jamanetwork.com/article.aspx?articleid=198503
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170	< 1% match (Internet from 30-Nov-2014) http://www.recentmedicalfindings.com/h93w/myopathy-of-critical-illness-5.html

- 171 < 1% match (Internet from 28-Mar-2012)
http://www.teida.lt/files/MOTOmed_straipsnis%20ICU.pdf
-
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<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2724770/pdf/nihms-126156.pdf>
-
- 173 < 1% match (Internet from 09-Sep-2009)
http://web.mac.com/mathieuraux/Mathieu/Mathieu_RAUX_MD_PhD_files/RPNB2008_SousPresse_Chiti.pdf
-
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<http://www.biomedcentral.com/1755-8794/2/2/>
-
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<http://aut.researchgateway.ac.nz/bitstream/handle/10292/1800/BMC%20published%20protocol.pdf?sequence=2>
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<http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2141.2011.08693.x/full>
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<http://www.nvic.nl/download.php?id=489>
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<http://www.medschool.soton.ac.uk/about/staff/listing/profile.asp?sth>
-
- 182 < 1% match (Internet from 30-Oct-2012)
<http://www.on.lung.ca.vs1.korax.net/Health-Care-Professionals/Ontario-Respiratory-Care-Society/downloads/UpdateSS07.pdf>
-
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<http://www.allfreeessays.com/topics/karen-leary-case-analysis/0>
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-
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-
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-
- 187 < 1% match (publications)
["Speaker Abstracts", Transfusion Medicine, 2013.](#)
-
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-
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-
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- 190 T. D. Mickleborough. "Inspiratory flow resistive loading improves respiratory muscle function and endurance capacity in recreational runners : Inspiratory muscle training and running". *Scandinavian Journal of Medicine and Science in Sports*. 06/16/2009
-
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Mark Watsford. "The Effects of Respiratory-Muscle Training on Exercise in Older Women." *Journal of Aging & Physical Activity*/10638652, 20080701
-
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-
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-
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-
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J-M. Boles. "Weaning from mechanical ventilation". *European Respiratory Journal*. 05/01/2007
-
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-
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-
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-
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-
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-
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-
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Submitted to Florida International University on 2009-11-20
-
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-
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-
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-
- 206 < 1% match (publications)
Jenkins, J.A, Josse, Andrea R, Bevene, J. "Fish-oil supplementation in patients with implantable cardioverter defibrillators: a meta-analysis (". *CMAJ: Canadian Medical*

Association Journ. Jan 15 2008 Issue

207 < 1% match (publications)

Palmieri-Smith, R. M., A. C. Thomas, C. Karvonen-Gutierrez, and M. Sowers. "A Clinical Trial of Neuromuscular Electrical Stimulation in Improving Quadriceps Muscle Strength and Activation Among Women With Mild and Moderate Osteoarthritis". *Physical Therapy*. 2010.

208 < 1% match (publications)

Berney, S., K. Haines, E. H. Skinner, and L. Denehy. "Safety and Feasibility of an Exercise Prescription Approach to Rehabilitation Across the Continuum of Care for Survivors of Critical Illness". *Physical Therapy*. 2012.

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USE OF THE INSPIRATORY MUSCLE TRAINER DEVICE (IMT) AFTER EXTUBATION IN A CRITICAL CARE SETTING Nthabiseng Veronica Thupana A dissertation

2submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in fulfilment of the requirements for the degree of Masters of Science in Physiotherapy. Johannesburg, 27 February 2015. Declaration: I, Nthabiseng Veronica Thupana, declare that this dissertation is my own work. It is being submitted for the degree of Masters of Science in Physiotherapy at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

Signature: _____ Date: _____ ABSTRACT
Background:

193Mechanical ventilation (MV) and intensive care unit (ICU)

admission are necessary medical interventions when required. However the effects of bed rest and immobility result in dysfunctions that occur within a very short period of time (Winkelman, 2007). The resultant diaphragmatic weakness results in weaning and extubation failure and may result in the need for re-intubation (Martin et al., 2013; Thille

173et al., 2013). In mechanically ventilated patients, inspiratory muscle

training (IMT) has been administered to decrease weaning failure by increasing diaphragmatic strength (Cader et al., 2010). The use of IMT during prolonged MV reportedly improved the perception of dyspnoea, six

81minute walk test (6MWT) and the ability to perform activities of daily living

(ADL) and the resultant