School of Physiotherapy

The effect of physiotherapy on the prevention and treatment of ventilator-associated pneumonia for intensive care patients with acquired brain injury

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Declaration

This thesis contains no material which has been accepted for the award of any other degree or diploma in any university.

To the best of my knowledge and belief this thesis contains no material previously published by any other person except where due acknowledgment has been made.

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Date: 31/8/05

Abstract

Background: Ventilator-associated pneumonia is a major cause of morbidity and mortality for patients in an intensive care unit. Once present, ventilator-associated pneumonia is known to increase the duration of mechanical ventilation, time in the intensive care unit, and length of hospital stay. Patients with acquired brain injury are commonly admitted to the intensive care unit and considered to be at a high risk for the development of respiratory complications such as ventilator-associated pneumonia, which could potentially impact on the intensive care unit costs and outcomes. Respiratory physiotherapy is often provided to prevent and/or treat ventilator-associated pneumonia in patients with acquired brain injury. The theoretical rationale of the respiratory physiotherapy is to improve airway clearance and enhance ventilation which may reduce the incidence of pulmonary infections and thus ventilator-associated pneumonia, and may in turn decrease the duration of mechanical ventilation, prevent the need for tracheostomy and hence result in reduced costs and shorter hospital stay. Although respiratory physiotherapy may be beneficial in reversing or preventing ventilator-associated pneumonia, to date there are no data concerning the effectiveness of respiratory physiotherapy in patients with acquired brain injury. Hence from an evidence-based perspective, at present there is no justification for the role of respiratory physiotherapy in the management of patients with acquired brain injury in the intensive care unit.

Aim: This two-part, prospective randomised controlled trial aimed to investigate the effect of regular prophylactic respiratory physiotherapy on the incidence of ventilator-associated pneumonia, duration of mechanical ventilation, and length of intensive care unit stay in adults with acquired brain injury, as compared to a control group (Part A). The second part of the study (Part B) randomised those subjects from Part A who developed a ventilator-associated pneumonia into a treatment or control group to establish if the provision of a regimen of regular respiratory physiotherapy influenced the outcome of ventilator-associated pneumonia. Additionally, this study also aimed to provide the first description of the financial costs of respiratory physiotherapy time in providing interventions to patients with acquired brain injury in the intensive care unit and investigated the cost effectiveness of respiratory physiotherapy interventions in decreasing the incidence of ventilator-associated pneumonia, duration of mechanical ventilation and length of intensive care unit stay.

Subjects: 144 adult patients with acquired brain injury admitted with a Glasgow Coma Scale of nine or less, requiring intracranial pressure monitoring, and invasive ventilatory support for greater than 24 hours, were randomised to a treatment group or a control group.

Methods: For subjects randomised to the treatment groups, the regimen of respiratory physiotherapy treatment was repeated six times per 24-hour period and continued until the subject was weaned from mechanical ventilatory support. Each respiratory physiotherapy

intervention of 30 minute duration comprised a regimen of positioning, manual hyperinflation and suctioning. In both Parts A and B, the control group received standard nursing and medical care but no respiratory physiotherapy interventions.

Results: Consent was obtained for 144 subjects, with 72 randomised for treatment in Part A. Part A groups were comparable with respect to demographic variables, with the exception of body mass index and gender distribution. Using intention to treat philosophy, there were no significant differences for incidence of ventilator-associated pneumonia [Treatment Group 14/72 (19.4%) vs. Control 19/72 (26.4%); $p = 0.32$], duration of mechanical ventilation (hr) [172.8 vs. 206.3); $p = 0.18$], or length of intensive care unit stay (hr) [224.2 vs. 256.4; $p = 0.22$].

For subjects with acquired brain injury receiving this prophylactic regimen of respiratory physiotherapy in the intensive care unit, in an attempt to prevent ventilator-associated pneumonia, the cost of physiotherapy was $487 per subject. Comparatively the intensive care unit mechanical ventilation bed day cost was $33,380 per subject. The cost of Part A respiratory physiotherapy time for Treatment Group 1 was 1.7 per cent of the cost of subject's intensive care unit mechanical ventilation bed days.

Thirty-three subjects (22.9%) from Part A developed ventilator-associated pneumonia, and were transferred to Part B and re-randomised, 17 to the Treatment Group 3. Part B groups were comparable with respect to demographic variables. No significant differences were detected in the dependent variables for Part B of the study, with similar duration of mechanical ventilation (hr) [342.0 vs. 351.0); $p = 0.89$], and length of ICU stay (hr) [384.7 vs. 397.9; $p = 0.84$] noted.

In those subjects with acquired brain injury in whom ventilator-associated pneumonia developed, the regimen of respiratory physiotherapy for the remaining duration of mechanical ventilation following diagnosis of ventilator-associated pneumonia costed an average of $788. Comparatively the intensive care unit bed day cost for the period of mechanical ventilation was $43,865. The cost of Part B respiratory physiotherapy time for Treatment Group 3 was 1.8 per cent of the cost of their intensive care unit mechanical ventilation bed days.

Subjects with a ventilator-associated pneumonia were significantly younger, were admitted with a lower Glasgow coma scale, and more likely to have been admitted with a chest injury than subjects without a ventilator-associated pneumonia. Duration of mechanical ventilation and length of intensive care unit stay were significantly increased in subjects with ventilator-associated pneumonia, but length of hospital stay was not significantly different. Significant differences in the costs of respiratory physiotherapy and intensive care unit mechanical ventilation bed day costs were evident between those subjects with ventilator-associated pneumonia as compared to those without ventilator-associated pneumonia. For subjects with ventilator-associated pneumonia, the respiratory physiotherapy time cost was $1,029 per

subject, compared to $510 for subjects without ventilator-associated pneumonia. The intensive care unit mechanical ventilation bed day cost for subjects with ventilator-associated pneumonia was $61,092 per subject, and $25,142 for those without a ventilator-associated pneumonia, giving an incremental health cost of $35,950 per episode of ventilator-associated pneumonia. No significant differences were evident in the cost of respiratory physiotherapy as a per cent of the cost of their intensive care unit mechanical ventilation bed days, with findings of 1.4 per cent in those with ventilator-associated pneumonia and 1.1 per cent in those without ventilator-associated pneumonia.

Conclusion: Use of a regular prophylactic respiratory physiotherapy regimen comprising of positioning, manual hyperinflation and suctioning, in addition to routine medical and nursing care, did not appear to prevent ventilator-associated pneumonia, reduce length of ventilation or intensive care unit stay in adults with acquired brain injury. Furthermore, in those acquired brain injury subjects with ventilator-associated pneumonia, regular respiratory physiotherapy did not appear to expedite recovery in terms of reducing length of ventilation or intensive care unit stay.

It can be concluded from the findings of this study that the presence of ventilator-associated pneumonia has a significant influence on morbidity and costs in subjects with acquired brain injury. Whilst statistically significant results were not found with clinical variables, it is suggested that the provision of a prophylactic respiratory physiotherapy regimen costing $487 per subject is a worthwhile investment in attempts to avoid the incremental health cost of $35,950 per episode of ventilator-associated pneumonia. In subjects with ventilator-associated pneumonia it is concluded that the cost of respiratory physiotherapy would not appear to be justified in attempts to reduce the duration of mechanical ventilation.

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Awarded a 2001 seeding grant from the Physiotherapy Research Foundation of the Australian Physiotherapy Association.

Patman, S., Stiller, K., Blackmore, M. & Jenkins, S. 2003, 'The effect of chest physiotherapy on the prevention and treatment of nosocomial pneumonia for intensive care patients with acquired brain injury - preliminary results', *Australian Journal of Physiotherapy,* vol. 49 e-AJP Electronic Supplement, p. 12.

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List of Abbreviations

ABG	arterial blood gas
ABI	acquired brain injury
APACHE	acute physiological and chronic health evaluation
ARDS	acute respiratory distress syndrome
ASA	American Society of Anaesthesia
BAL	broncho-alveolar lavage
BMI	body mass index
COPD	chronic obstructive pulmonary disease
CPIS	clinical pulmonary infection score
CPP	cerebral perfusion pressure
CT	computerised tomography
CXR	chest x-ray
ETA	endotracheal aspirate
ETT	endotracheal tube
FiO_2	fraction of inspired oxygen
GADP	gravity-assisted drainage position
GCS	Glasgow Coma Scale
H_2	histamine type 2
HME	heat-moisture exchanger
HR	heart rate
ICP	intracranial pressure
ICU	intensive care unit
NBL	non broncho-alveolar lavage
MAP	mean arterial pressure
MH	manual hyperinflation
MV	mechanical ventilation
NP	nosocomial pneumonia
O_2	oxygen
$PaCO_2$	arterial carbon dioxide tension
PaO_2	arterial oxygen tension
PEEP	positive end expiratory pressure
PSB	protected specimen brush
RPH	Royal Perth Hospital
SAPS	simplified acute physiological score
USA	United States of America
VAP	ventilator-associated pneumonia
vs.	versus
WA	Western Australia

Unit of measurement

cmH_2O	centimetres of water
hr	hour
mg	milligram
ml	millilitre
mmHg	millimetres of Mercury
°C	degrees Celsius
$	dollar
AUD$	Australian dollars
DM	Deutschmark
US$	American dollars

Statistical terms and symbols

α	alpha level
χ^2	Chi-Square test
d	effect size index for the t-test
df	degrees of freedom
F	test statistic for the analysis of variance
n	number of subjects
p	probability value
SD	standard deviation
Sig.	significance level
Std	standard
t	test statistic for the comparison of two means
%	per cent
<	less than
≤	less than or equal to
>	greater than
≥	greater than or equal to

Chapter 1 Introduction

This chapter outlines the research problem and its significance, along with the research question, the study aim, and the approach adopted to address the research question.

1.1 Research Problem

Ventilator-associated pneumonia (VAP) is a major cause of morbidity and mortality for patients in an intensive care unit (ICU). Numerous controversies exist regarding VAP, with no uniform standards existing for the diagnosis, prevention or management of VAP. As a consequence various, often conflicting, recommendations for the bedside management of patients with VAP exist.

Patients with acquired brain injury (ABI) are commonly admitted to the ICU and considered to be at a high risk for the development of respiratory complications such as VAP. Although respiratory physiotherapy for patients with ABI may be beneficial in reversing or preventing VAP, to date there are no data concerning the clinical or cost effectiveness of respiratory physiotherapy in patients with ABI. Hence from an evidence-based perspective, at present there is no justification for the role of respiratory physiotherapy in the management of patients with ABI in the ICU.

1.2 Significance

Ventilator-associated pneumonia is a frequent and severe complication occurring in patients treated with mechanical ventilation (MV). Pneumonia results from microbial invasion of the normally sterile lower respiratory tract. The majority of infections appear to result from aspiration of potential pathogens that have colonised the oropharyngeal airway. Once present, VAP is known to increase the duration of MV, time in the ICU, and length of hospital stay. There is a substantial cohort of patients admitted to ICU following ABI that may acquire VAP, which could potentially impact on ICU costs and outcomes. It has been widely demonstrated that VAP results in significant increased costs to the health care system, and patients with VAP have an increased risk of morbidity and mortality arising from an episode of VAP, particularly in the presence of an ABI.

Respiratory physiotherapy interventions are a relatively inexpensive and widely available management strategy that may benefit patients in the ICU by influencing the incidence of VAP and its associated morbidity. Theoretically, respiratory physiotherapy aims to improve airway clearance and enhance ventilation which may reduce the incidence of pulmonary infections and thus VAP. Thus, respiratory physiotherapy may decrease the duration of MV, prevent the need for tracheostomy and hence result in reduced costs and shorter hospital stay. Conversely it has been shown that respiratory physiotherapy may cause marked changes, albeit temporary, in intracranial and haemodynamic variables in patients with ABI. To date there are no data concerning the effectiveness of respiratory physiotherapy in

preventing or treating the pulmonary conditions occurring in patients with ABI admitted to the ICU.

The intention of this study was to provide justification for the role of respiratory physiotherapy in preventing and treating VAP for patients with ABI in ICU. By also conducting an economic evaluation, this study aimed to determine any cost savings obtained from improved patient outcomes resulting from physiotherapy intervention. As the role of respiratory physiotherapy for patients with ABI, with or without VAP, is presently not evidence-based, study results and economic analyses have significant implications for establishing physiotherapy efficacy, staffing requirements and service provision. Study results may in turn facilitate elimination of one potential conflicting recommendation for the bedside management of patients with ABI, that is, whether or not to provide respiratory physiotherapy as part of preventative or management strategies for VAP.

1.3 Research Question and Aim

It remains unclear whether there is any role for respiratory physiotherapy in the prevention and treatment of VAP in the patient with ABI in the ICU. Therefore, this study aimed to provide the first comprehensive objective evaluation of the effectiveness of respiratory physiotherapy services for patients admitted to the ICU with ABI by:

- Investigating the clinical effectiveness and cost effectiveness of respiratory physiotherapy interventions in altering the incidence of VAP and other important clinical outcomes, such as duration of MV and length of ICU stay.
- Providing justification of respiratory physiotherapy service provision to the ICU in terms of clinical effectiveness and cost effectiveness for patients with VAP following ABI.
- Providing validation of the required level of respiratory physiotherapy services and staffing in the ICU based on clinical outcomes and economic grounds.

1.4 Approach Adopted

A two-part, prospective randomised controlled trial to investigate the effects of respiratory physiotherapy for patients with ABI admitted to the ICU at Royal Perth Hospital (RPH) was undertaken. The aim of Part A of the study was to establish if the provision of regular prophylactic respiratory physiotherapy (six interventions per 24-hours) influenced the incidence of VAP, as compared to a Control Group. The second part of the study (Part B) randomised those subjects from Part A who fulfilled the criteria for VAP into a Treatment (six interventions per 24-hours) or Control Group to establish if the provision of a regimen of regular respiratory physiotherapy influenced the outcome of VAP. In both Parts A and B, the Control Group received standard nursing and medical care but no respiratory physiotherapy interventions.

Additionally an economic analysis for Part A of the study evaluated the 'cost per VAP subject

prevented' in which the physiotherapy costs for subjects to the point when the subject was weaned from mechanical ventilatory support were determined.

In Part B, costs of intervention were to be determined, with the aim of establishing cost effectiveness ratios for the provision of regular respiratory physiotherapy, based on the following outcomes: ventilated bed day reduced, hospital ICU bed day reduced, and life year gained. The aim was to determine predicted savings based on the cost of ICU bed days reduced.

Chapter 2 Literature Review

This chapter provides a review of the background literature and is divided into three main sections. The first section relates to VAP, and discusses its definition, incidence, significance, pathogenesis, risk factors, diagnosis, prevention and management. The second section focuses on ABI and includes definition, incidence, and management, and concludes with a discussion of the relationship of ABI with VAP. The third section describes respiratory physiotherapy, its role in the ICU and in particular for patients with VAP, along with a review of the evidence for respiratory physiotherapy in VAP and ABI. Finally a short summary is provided outlining the current state of knowledge relating to the role of respiratory physiotherapy in the management of patients with ABI in preventing and/or treating VAP, thereby providing justification for the present investigation.

2.1 Ventilator-Associated Pneumonia

2.1.1 Definition

Nosocomial pneumonia (NP) is defined as infection of lung parenchyma of the lower respiratory tract that was neither present nor developing at the time of hospital admission (Bergogne-Berezin 1995; Craven & Steger 1995; Craven et al. 1998; Garner et al. 1988). The term VAP has been introduced to represent the subgroup of patients who develop NP during MV (Coalson 1995) and specifically refers to NP developing in mechanically ventilated patients following 48-hours of intubation (Bauer et al. 2000; Chastre & Fagon 2002; Kollef 1999b). Further differentiation of NP and VAP are described in the literature; the use of the terms 'early onset' and 'late onset' are common, although definitions have not been standardised (Ewig et al. 2002). Early onset is described as NP or VAP that appears within the first three to four days of MV (Antonelli et al. 1994; Pingleton et al. 1992), whilst late onset refers to VAP developing after three to five days of MV (American Thoracic Society 1996; Bauer et al. 2000; Craven et al. 1997; Grossman & Fein 2000; Pingleton et al. 1992). Early onset VAP is most often reported to be due to antibiotic sensitive pathogens such as *Haemophilus influenzae*, *Staphylococcus aureus* and *Streptococcus pneumoniae*, and is associated with a better prognosis than late onset VAP which is frequently attributable to antibiotic resistant pathogens such as *Pseudomonas aeruginosa*, *Acintobacters* and *Enterobacters* (Chastre & Fagon 2002; Craven 2000; Hubmayr 2002; Ibrahim et al. 2000; Kollef 1999b).

2.1.2 Incidence

Nosocomial pneumonia is the second most common hospital acquired infection (Bergogne-Berezin 1995; Celis et al. 1988) and the most common infection in the ICU (George 1995; Vincent et al. 1995; Vincent 2004). The rate of NP is higher for patients in ICU than for non-ICU patients (Chastre & Fagon 2002; Rello et al. 2001), with as much as a 20-fold increase in patients who are mechanically ventilated compared to those who are not (American

Thoracic Society 1996; Rello et al. 2001). Nosocomial pneumonia is said to account for 18 per cent of all nosocomial infections (Bergogne-Berezin 1995; Craven & Steger 1995; Craven et al. 1998) and VAP accounts for up to 90 per cent of infections in patients requiring MV (Cook et al. 1998b; Vincent 2004).The largest reported ICU prevalence study revealed that on the day of the study, 45 per cent of patients in ICU in Europe had infections, with almost half caused by VAP (Vincent et al. 1995). In the USA, the National Nosocomial Infection Surveillance data showed that 27 per cent of all nosocomial infections in medical ICUs were due to pneumonia, with 86 per cent of NP associated with MV (Richards et al. 1999). Similarly, in combined medical-surgical ICUs, 31 per cent of infections were NP, with 83 per cent of NP associated with MV (Richards et al. 2000). Rates of VAP are generally higher in surgical compared to medical ICUs. The Canadian critical care trials group reported that 18 per cent of patients developed VAP on average nine days after ICU admission (Cook et al. 1998b). From these major studies it is apparent that NP and VAP are significant issues within the ICU and incidence rates vary considerably.

Accurate data on the epidemiology of VAP are limited by the lack of standardised criteria and definitions for its diagnosis. There are major limitations to epidemiological studies of ICU acquired pneumonias due to the failure to distinguish between NP and VAP, and the variation in terminology, criteria and definitions used for diagnosis (Hubmayr 2002). Additionally, significant variations such as the setting and case-mix of study centres, and the divergent susceptibility patterns of pathogens in different ICUs, impact on the epidemiology of VAP (Cook 2000).

Previous studies have reported an incidence of VAP varying from 10 to 40 per cent among mechanically ventilated patients, with rates of 20 to 25 per cent in the majority of reports (Chastre & Fagon 2002; Craven et al. 1986; Eggimann et al. 2003; Jimenez et al. 1989; Kollef 1993; Sofianou et al. 2000; Torres et al. 1990; Torres et al. 1999; Vosylius et al. 2003). The cumulative risk for developing VAP is related to the duration of MV with rates rising one to three per cent per day of intubation and MV (Craven et al. 1998; Rello et al. 2001; Torres et al. 1999). This risk is greatest early in the hospital stay (three per cent per day during the first five days) and decreases after two weeks (to one per cent per day or less) (Cook & Kollef 1998). Early onset VAP may account for as many as 50 per cent of cases of VAP (Cook 2000).

In addition to the use of 'percentage of patients on MV acquiring VAP' as a method of reporting the incidence of VAP, some literature refers to 'frequency of episodes per patient days' or 'per ventilation days' as an alternative way of describing the incidence of VAP. Depending on the population studied, VAP is reported to range from six to 52 cases per 100 patients in ICU, but it is suggested that using an index of 'rates per 1000 ventilator days' provides the best comparison (Craven 2000). Overall within the general ICU population, VAP rates are most commonly reported to be 10 to 15 cases per 1000 ventilator days, with ratios

generally higher in surgical compared to medical patients (Cook et al. 1998b; Craven et al. 1998; George 1995; Torres et al. 1999). Rates vary from 2.9 cases per 1000 ventilator days for paediatric patients through to 34.4 cases per 1000 ventilator days for those admitted with thermal injuries (A report from the NNIS System 2003; George 1995). Most recently, neurosurgical ICU VAP rates were reported as being 12.9 cases per 1000 ventilator days (A report from the NNIS System 2003).

Despite the lack of standardisation and consensus with definitions and reporting mechanisms it is apparent that VAP is a significant complicating factor for many patients in the ICU.

2.1.3 Significance

Ventilated-associated pneumonia is associated with increases in duration of MV, prolonged length of ICU and hospital stay, increased hospital mortality rates and may substantially increase the cost of hospitalisation two to three-fold.

2.1.3.a Morbidity

Ventilator-associated pneumonia is the most common nosocomial infection in ICU and is coupled with high morbidity and mortality (American Thoracic Society 1996). Ventilator-associated pneumonia is associated with prolonged MV, with reported mean MV duration increases of 5.0 to in excess of 22.0 days when VAP develops in the general ICU population (Cook et al. 1998a; Dietrich et al. 2002; Jimenez et al. 1989; Rodriguez et al. 1991). Ewig et al (1999) found no differences in a general ICU population with early onset VAP in the duration of MV, but increased MV duration from 5.5 days to 10.1 days in those with late onset VAP. When reporting the influence of VAP on duration of MV in neurosurgical/neurological ICUs, Dietrich et al (2002) found no greater duration of MV to that observed in the general ICU population who developed VAP.

In addition to increased duration of MV, many authors have reported that VAP significantly increases length of stay in ICU. In the general ICU population, increased mean length of ICU stay attributable to VAP of between 4.0 and 21.0 days is reported (Bercault & Boulain 2001; Cook 2000; Dietrich et al. 2002; Heyland et al. 1999; Hugonnet et al. 2004; Rodriguez et al. 1991). Other authors report overall length of hospital stay increasing up to 34.0 days for those with VAP (Cook et al. 1998b; Fagon et al. 1993; Hugonnet et al. 2004; Warren et al. 2003), and from a mean of 3.5 to 10.3 days with early onset VAP or a mean of 21.0 days with late onset VAP (Ibrahim et al. 2000). However, Ewig et al (1999) reported no significant difference in length of ICU stay with early onset VAP, but found late onset VAP increased ICU stay from a mean of 8.0 to 14.0 days.

When specifically examining the ABI population, Hsieh et al (1992) found the majority of VAP occurred within the first three days of admission and reported a significant mean difference in length of ICU stay from 7.2 days for non-VAP patients to 10.5 days for those who

developed VAP. Dietrich et al (2002) and Combes et al (2000) found that VAP in patients with ABI increased ICU length of stay by 14.0 and 16.8 days respectively. Dietrich et al (2002) also found that in neurosurgical/neurological ICUs, an ICU stay of greater than 30 days was more common in patients with VAP.

Not only does VAP influence morbidity by increasing MV duration and length of ICU stay, but also significantly prolongs hospital stay. George (1995) summarised that the increased hospital stay attributable to VAP ranged from 4.0 to 13.0 days with a median of 7.6 days, whilst the American Thoracic Society (1996) documented that an average increase of 7.0 to 9.0 days occurred. Increased mean length of hospital stay from 10.5 days in non-VAP patients to 38.0 days in patients with VAP (Rello et al. 1992; Warren et al. 2003), and from means of 11.8 up to 33.3 days with early onset VAP or 37.2 with late onset VAP (Ibrahim et al. 2000) have been reported. In patients with ABI, Hsieh et al (1992) reported a significant mean difference in actual length of hospital stay from 22.5 days for patients without VAP to 34.8 days for those who developed VAP, whilst Dietrich et al (2002) also found that a mean of 10.1 more days in hospital were required in those with VAP in neurosurgical/neurological ICUs.

As noted previously, the lack of standardisation and consensus with definitions and reporting mechanisms contributes significantly to the variation in results reported, thereby confounding interpretation.

2.1.3.b Mortality

Nosocomial pneumonia independently contributes to patient mortality in ICU (Fagon et al. 1996), with the mortality attributable to VAP ranging from 25 to 33 per cent (Chastre et al. 1995; Cook 2000; George 1995). In other words, one quarter to one third of patients in ICU who develop VAP and die would not have died otherwise (George 1995). A risk ratio for death associated with VAP of 2.1 and 2.0 has been reported (Bercault & Boulain 2001; Fagon et al. 1993), which rises to 2.6 when attributable to multi-resistant micro-organisms (Bercault & Boulain 2001). Mortality rates for nosocomial infections in total are approximately one to four per cent but this can range from 20 to 50 per cent for VAP and even as high as 76 per cent in some specific settings or with high risk pathogens (Chastre & Fagon 2002). Mortality rates are reported as rising from 8.5 per cent for non-VAP patients to as high as 55.0 per cent in those with VAP (Celis et al. 1988; Craven et al. 1986; Kollef 1993; Torres et al. 1990; Warren et al. 2003). Ewig et al (1999) found no differences in mortality between patients with or without VAP regardless of whether it was early or late onset. In addition to the lack of standardisation and consensus with definitions, the difficulty of establishing a firm diagnosis of VAP (Section 2.1.6) could explain the disparate figures for the incidence of VAP and the associated mortality rates (Fagon et al. 1996).

2.1.3.c Financial costs

It is not possible to evaluate precisely the morbidity and costs associated with VAP (Chastre

& Fagon 2002). However, VAP may substantially increase the cost of hospitalisation two to three-fold (Craven et al. 1998) by lengthening the duration of MV, time in ICU, and overall length of hospital stay. The prolonged periods of hospitalisation, as outlined in Section 2.1.3a, underscore the considerable financial burden that arises from the development of VAP, but there are very little data or evaluation in the form of cost analysis of VAP.

In the USA the annual financial cost of diagnosing and treating NP is reported to range from US$1.2 billion (Kaye et al. 2000), to greater than US$2 billion (Craven et al. 1992). It has been estimated that as much as US$20,000 per VAP episode is added to hospital costs, and in terms of financial cost, prevention of VAP may be better than effective treatment and cure (Niederman 2001). Other authors have reported that VAP increased costs by up to US$48,948 per episode (Hugonnet et al. 2004; Rello et al. 2002b; Warren et al. 2003). Warren et al (2003) presented further unadjusted cost comparisons suggesting that early onset VAP resulted in median total costs of hospitalisation of US$36,822 compared with US$60,562 in the case of late onset VAP. Dietrich et al (2002) reported costs per patient with VAP amounted to DM 14,606 (US$9,260 equivalent). In patients with ABI, Dietrich et al (2002) determined the excess costs associated with VAP to be DM 29,610 (US$18,770 equivalent). An estimated cost savings of US$13,340 for every episode of VAP that is prevented has been reported (van Nieuwenhoven et al. 2004). The difficulty of establishing a firm diagnosis of VAP, in addition to the lack of standardisation and consensus with definitions and inclusions for cost determination, could explain the disparate figures for the financial cost of VAP.

In summary, patients with VAP have a significantly longer duration of MV, length of ICU and hospital stay, with higher mortality rates and hospital costs when compared with patients without VAP.

2.1.4 Pathogenesis

A detailed description of the pathogenesis of VAP is beyond the scope of this thesis; therefore a brief synopsis only is provided. Three recent publications provide comprehensive reviews of VAP pathogenesis (Chastre & Fagon 2002; Mehta & Niederman 2003; Rumbak 2002).

Under normal circumstances the lower respiratory tract is kept relatively sterile by a number of protective mechanisms. Inhaled air is filtered by the nasopharyngeal mucosa, the integrity of the epiglottic barrier prevents significant aspiration, and the pulmonary defences attempt to destroy any organisms that are aspirated (Rumbak 2002). There are only four routes through which bacteria can reach the lower respiratory tract to cause the development of VAP: inhalation, aspiration, hematogenous spread, and contiguous spread (Rello & Diaz 2003). Pneumonia develops when virulent organisms reach the lower airways and overwhelm the lung defences of the host. A local inflammatory response occurs, with the accumulation of neutrophils and other effector cells in the peripheral bronchi and alveolar

spaces; this may be manifested clinically by purulent sputum, lung infiltrates, fever, and leukocytosis (Meduri & Johanson 1992).

Colonisation of the upper airway and stomach plays a major role in the development of VAP and precedes invasive infection (Bonten et al. 2004; Mehta & Niederman 2003; van Nieuwenhoven et al. 2004). Most VAPs result when micro-organisms are aspirated into the lung from a previously colonised oropharynx. Endotracheal intubation is the most important risk factor in the pathogenesis of VAP because it impairs local host defence mechanisms, creates binding sites for bacteria, and allows for the formation of biofilms that may serve as reservoirs of bacteria (Mehta & Niederman 2003). The endotracheal tube (ETT) per se can contribute to VAP pathogenesis by allowing direct entry of bacteria into the lungs, by elimination or suppression of the cough reflex, and by providing a surface for the formation of a bacterial biofilm along the inside of the ETT. Intubation also facilitates the entry of bacteria into the lungs by pooling and leaking of contaminated secretions around the ETT cuff (American Thoracic Society 1996; Craven & Steger 1996). Organisms that reach the inside of the ETT can proliferate easily because this site is not protected by host defences, and antibiotics do not penetrate this region (Mehta & Niederman 2003). The source of the bacteria that colonise the upper airway is most likely the patient's own intestinal flora, but also other patients, health care staff, or other environmental sources can transmit flora to patients (Lustbader et al. 2001).

2.1.5 Risk factors

There is an extensive body of literature devoted to the epidemiology of risk factors associated with the development of VAP. Several recent articles provide further detail of VAP risk factors (Bauer et al. 2000; Chastre & Fagon 2002; Cook & Kollef 1998; Fleming et al. 2001; Kollef 1999b; Vincent et al. 2001). This section provides a brief overview of this complex and controversial topic.

Risk factors for the development of VAP are varied and dependent on factors such as prior antimicrobial therapy, duration of hospital stay and the population of the ICU (Chastre & Fagon 2002). Risk factors can be globally divided into four categories: host factors and underlying disease, factors that enhance colonisation of the oropharynx and stomach (such as antibiotics and hospitalisation in ICU), factors that increase the risk of aspiration of nosocomial pathogens into the lower respiratory tract, and devices or equipment that interrupt natural host defences (Craven & Steger 1995); or more simply into two categories: intrinsic and extrinsic risk factors (Bauer et al. 2000). Table 2.1 summarises the main risk factors for VAP, adapted from published literature (Bauer et al. 2000; Bonten et al. 2004; Craven & Steger 1996; Torres et al. 1999).

Table 2.1 Summary of risk factors for nosocomial pneumonia and ventilator-associated pneumonia

Risk factor category	Univariate risk factors for pneumonia	Independent risk factors for NP	Independent risk factors for VAP
Host factors and underlying disease	Age > 60 years	Age > 60 years	Age > 60 years
	SAPS > 9	APACHE II score > 16	Organ failure
	Head trauma	Trauma / head injury	
	No prior surgery	Upper abdominal / thoracic surgery	
	Underlying disease	Neuromuscular disease	
	Alcohol intake	Low serum albumin	
	COPD		COPD / PEEP / pulmonary disease
	Coma		Coma / impaired conscious state
	ASA class IV		
	Renal failure		
	Smoking		
Factors that enhance colonisation	Prior care facility	Bronchoscopy	Therapeutic interventions
	Continuous enteral feeding		Gastric colonisation and pH
	Prior antibiotics		Prior antibiotics
	H_2-Blockers or antacids vs. sucralfate		H_2-Blocker and antacids
	Aspiration before intubation		Season – autumn, winter
Factors that increase risk of aspiration	MV > 2 days	ETT intubation	MV > 2 days
	Chemical paralysis		Large volume gastric aspiration
	Nosocomial maxillary sinusitis		Supine head position
	FiO_2 > 0.50		Reintubation
Devices or equipment	Airway instrumentation	Nasogastric tube	Ventilator circuit changes 24 vs. 48 hr
	Intra-aortic balloon pump		Intracranial pressure monitor
	Tracheostomy		Tracheostomy
	Cascade humidifier vs. HME		

NP = nosocomial pneumonia; VAP = ventilator-associated pneumonia; SAPS = Simplified Acute Physiological Score; APACHE II = Acute Physiological and Chronic Health Evaluation score; COPD = chronic obstructive pulmonary disease; PEEP = positive end expiratory pressure; Prior care facility = location of medical intervention and/or hospitalisation preceding intensive care stay; ASA = American Society of Anaesthesia; H_2 = histamine type 2; MV = mechanical ventilation; ETT = endotracheal tube; FiO_2 = fraction of inspired oxygen; hr = hour; vs. = versus; HME = heat-moisture exchanger.

Risk factors that are widely acknowledged as being specifically relevant and associated with the development of VAP in the study population in this thesis, patients with ABI are those:

- admitted with head trauma / ABI [and in particular a Glasgow coma scale (GCS) < 9] (Antonelli et al. 1994; Berrouane et al. 1998; Bonten et al. 2004; Celis et al. 1988; Chevret et al. 1993; Ewig et al. 1999; Harris et al. 2000; Helling et al. 1988; Hsieh et al. 1992; Rello et al. 1992),
- requiring prolonged MV (Antonelli et al. 1994; Lynch 2001; Mosconi et al. 1991; Nadal et al. 1995; Torres et al. 1990),
- positioned in supine (Drakulovic et al. 1999; Kollef 1993), and
- requiring use of intracranial pressure (ICP) monitoring (Antonelli et al. 1994; Bonten et al. 2004; Craven et al. 1986; Harris et al. 2000).

2.1.6 Diagnosis

The area dominating recent VAP literature pertains to the issue of diagnosis. At present there is no well accepted 'gold-standard' against which the various diagnostic strategies can be compared (Bowton 1999; Chastre & Fagon 2002; Craven 2000; Ewig et al. 2002; Ibrahim et al. 2000; Pingleton et al. 1992; Rello et al. 2001; Waterer & Wunderink 2001). Rather, there are a variety of diagnostic procedures with varying sensitivity and specificity (Craven 2000; Pingleton et al. 1992; Wood et al. 2003). The lack of consensus regarding the best way to diagnose VAP explains, in part, why incidence rates vary so widely from five to greater than 50 per cent of patients receiving MV (Torres & Carlet 2001).

Essentially VAP can be diagnosed in three ways: using clinical criteria, non-invasive methods, and invasive techniques.

2.1.6.a Clinical criteria

Diagnosis of VAP using clinical criteria has included combinations of new and persistent infiltrates on chest radiography with two of the following three criteria: fever (>38.3° C), leukocytosis (> 12 x 10^9 cells/ml), and/or presence of purulent tracheal secretions (Johanson et al. 1972). Other clinically based diagnostic criteria commonly reported in the literature include those from the Centre for Disease Control (Garner et al. 1988) and the American College of Chest Physicians- American Thoracic Society consensus conferences (Hernandez & Rello 2003). It has been suggested that these conventional clinical criteria alone are both insensitive and non-specific for diagnosing VAP in the mechanically ventilated patient (A'Court & Garrard 1992; Brun-Buisson 1995; Fagon et al. 1993; Kirtland et al. 1997). In ventilated patients, systemic signs of infection and/or lung infiltrates are frequently due to causes other than lung infection. Fever and leukocytosis may be the consequence of any condition that releases cytokines, including non-infectious origins, such as drug related fever, pulmonary oedema or infarction, and non-pulmonary infections such as vascular catheter

infection (e.g. associated with arterial and central venous indwelling catheters), gastrointestinal infection, urinary tract infection, post-operative fever, sinusitis, or wound infection (Fagon & Chastre 2003). Similarly, purulent secretions are almost inevitably found in patients receiving prolonged MV and do not specifically indicate the presence of pneumonia.

The greatest limitation of the available literature is the almost uniform reliance on non-specific clinical and radiological criteria to define cases of VAP. These conventional clinical criteria have been unable to reliably diagnose cases of VAP documented by autopsy, histopathology and other stringent approaches (George 1995; Kirtland et al. 1997) and are associated with 30-35 per cent false-negative and 20–25 per cent false-positive results (Fabregas et al. 1999). The clinical diagnosis leads to the overestimation of the incidence of VAP because cases of tracheobronchial colonisation and non-infectious processes mimicking VAP are included (Fagon et al. 2000). As a result of the non-specificity of a diagnostic strategy based on clinical evaluation alone, many patients receive unnecessary antibiotics which exposes them to unnecessary toxicity, increased hospital costs, favours the emergence of resistant micro-organisms and limits the search for the true aetiology of the suspected infection (Fagon et al. 2000; Mariscal et al. 2001).

2.1.6.b Non-invasive methods

The use of simple non-invasive semi-quantitative techniques such as cultures of endotracheal aspirates (ETA) is widely reported as a diagnostic strategy in patients with a suspicion of VAP. The ETA is simple and inexpensive to obtain, with minimal training required (Cook & Mandell 2000; Ioanas et al. 2001; Torres & Ewig 2004b). Cook and Mandell (2000) reported that in studies using ETA cultures, sensitivity ranged from 38-100 per cent and specificity ranged from 14-100 per cent. They suggested that studies of cultures of ETA varied widely in the ability to diagnose VAP and therefore yielded insufficient data to generate strong clinical policy recommendations. Used in isolation, non-invasive diagnostic tools (such as the ETA) are more specific than clinical diagnosis and achieve diagnostic performances very similar to invasive means, with a slight decrease in specificity which is of questionable clinical relevance (Ewig & Torres 2001; Wu et al. 2002). Quantitative ETA cultures may be an adequate tool for diagnosing VAP when invasive techniques are unavailable (Aucar et al. 2003), but this technique has several potential limitations including the potential for sampling errors inherent in a blind technique when the airway cannot be visualised (Chastre & Fagon 2002; Mariscal et al. 2001).

Clinical criteria are considered to be useful in identifying suspected cases of VAP (Ewig et al. 1999; Flanagan et al. 2000; Grossman & Fein 2000; Wunderink 2000), but when combined or accompanied with microbiological criteria are more likely to assist the confirmation of a diagnosis of VAP (Brun-Buisson 1995; Fartoukh et al. 2002; Ewig et al. 1999; Garrard & A'Court 1995; Luyt et al. 2004; Mentec et al. 2004; Torres & Ewig 2004a). The clinical

pulmonary infection score (CPIS) described by Pugin et al (1991) combines weighted indices of clinical and physiological variables with microbiological ETA results (Table 3.2 and Section 3.5.3 outline full details of the CPIS). The predictive value of the CPIS for the diagnosis of VAP approaches that of bronchoscopic criteria (Pugin et al. 1991; Pugin 2002). The CPIS, at a threshold score of six, achieved 72 per cent sensitivity and 85 per cent specificity in a post-mortem study (Papazian et al. 1995). A modified CPIS scoring system, when combined with non-directed bronchial lavage, demonstrated the development of VAP (A'Court et al. 1993; Fartoukh et al. 2002; Fartoukh et al. 2003; Garrard & A'Court 1995). This suggests that the use of serial microbiological surveillance cultures and the CPIS are valuable methods for diagnosing VAP. However in most cases the complete CPIS can be calculated only in retrospect, after VAP is suspected clinically (Wunderink 2000).

2.1.6.c Invasive techniques

The role of invasive and quantitative culture techniques such as broncho-alveolar lavage (BAL) and protected-specimen brush (PSB) in the diagnosis of VAP, whilst used to supplement clinical judgement, is controversial (Grossman & Fein 2000; Mentec et al. 2004). These invasive techniques were designed to avoid the colonising flora of the upper airway contaminating the lower airway culture (Ioanas et al. 2001), but because of the necessity of passing through the upper respiratory tract in order to reach the lower respiratory tract, invasive techniques are still subject to potential contamination (Chastre & Fagon 2002; Mariscal et al. 2001). Studies have demonstrated that BAL and PSB have a sensitivity and specificity greater than 80 per cent, with the BAL being more sensitive and the PSB more specific in diagnosing VAP (Hubmayr 2002). However, performance of invasive techniques such as these require specialised equipment, highly trained staff, and are not without risk of significant complications. The cost effectiveness of invasive versus non-invasive diagnostic strategies has not been established (Hubmayr 2002; Torres & Ewig 2004b) and an invasive approach has not been shown to alter mortality (Rello et al. 2004; Sherner et al. 2004). Despite two decades of research, there is still no evidence that invasive techniques should form part of the routine approach to the diagnosis of suspected VAP (Ewig & Torres 2002).

2.1.6.d Diagnosis summary

Reviewing the literature, it is possible to find publications to support all the standard techniques and approaches to VAP diagnosis. However, diagnosis of VAP remains a controversial issue, with variation in approaches potentially associated with misclassification bias, and use of different diagnostic strategies resulting in different infection rates (Eggimann et al. 2003). No difference exists between the sampling techniques in terms of reliability or in obtaining clinically significant pathogens (Aucar et al. 2003; Wood et al. 2003), and to date no study has demonstrated the superiority of a specific diagnostic method in terms of a lower incidence of complications, better patient outcomes, or reduced hospital costs (Craven 2000; Torres & Ewig 2004b). Individual local settings act as systematic confounders to the

incidence and diagnosis of VAP. Because of local bacteriological epidemiology, divergent susceptibility patterns of pathogens in the ICU, different antibiotic regimens, and variations in microbial and/or histological work-up, each ICU setting should establish its own preferred diagnostic techniques (Ewig 1996; Vincent 2004).

For the purpose of this study, a diagnostic algorithm, based on that of Grossman and Fein (2000), was used to diagnose and determine the incidence of VAP. Initially the suspicion of VAP, based on a threshold score of seven or greater, was identified through the daily use of the CPIS (Table 3.2). In suspected cases of VAP, quantitative testing in the form of non-bronchoscopic lavage (NBL) was then used to confirm the diagnosis and aetiology of the VAP.

2.1.7 Prevention

Prevention and management of VAP are integrally entwined; many preventative strategies also form part of the management to restrict the impact of VAP and are of critical importance for risk reduction, improvement in patient outcome, and reduction in hospital costs. To date, few interventions have been shown to be beneficial in the prevention of VAP (Hubmayr 2002). Prophylactic strategies should include an effective infection control programme, semi-upright positioning of the patient, judicious use of enteral feeding, reduction of the inappropriate use of antibiotics, and removal of unnecessary invasive devices (Cook et al. 2002; Craven et al. 2002; Kollef 2004; Vincent 2004; Zack et al. 2002). Foremost in the literature on VAP prevention are effective infection control practices and procedures. These infection control practices can be grouped into three categories (Bergogne-Berezin 1995):

- methods to eliminate endogenous pathogens and reduce oropharyngeal and intestinal colonisation,
- methods to prevent cross contamination and other environmental sources of contamination (e.g. cleaning of respiratory equipment, appropriate hand washing and isolation procedures), and
- antibiotic prophylaxis in post-operative high risk patients.

The use of a multidisciplinary team approach focussing on educational measures has been shown to be effective in reducing or limiting further rises in VAP rates (Babcock et al. 2004; Kaye et al. 2000; Kollef 1999a; Rello et al. 2002a; Salahuddin et al. 2004; Zack et al. 2002).

Recently, Collard, Saint and Matthay (2003) and Kollef (2004) published reviews on methods for preventing VAP and concluded that avoidance of unnecessary antibiotics, semi-recumbent as opposed to supine positioning, sucralfate rather than histamine type 2 antagonists for stress ulcer prophylaxis, and selective digestive tract decontamination had the strongest supporting evidence. Aspiration of subglottic secretions and the use of oscillating beds may be useful in select populations but there is no evidence to support specific methods of enteral feeding or more frequent changing of the ventilator circuit (Collard et al. 2003; Dezfulian et al. 2005; Dodek et al. 2004).

In a review by Mehta and Niederman (2003) a 10 point strategy for VAP prevention was proposed (Table 2.2).

Table 2.2 Strategies for prevention of VAP

1.	Proper patient position in semi-erect; avoid supine position
2.	Using an ETT that allows for subglottic drainage
3.	Maintaining adequate ETT cuff pressures to prevent aspiration of pooled secretions
4.	Monitoring for excess gastric residuals that lead to aspiration
5.	Small bowel feeding whenever possible (to avoid aspiration, bacterial translocation)
6.	Careful handling of ventilator circuits to avoid washing condensate back to patient
7.	Using non-invasive positive pressure ventilation rather than intubation whenever possible
8.	Potential antibiotic interventions, such as use of 24 hours of antibiotic therapy for patients with witnessed aspiration; antibiotic rotation
9.	Possible role of selective digestive decontamination; oropharyngeal decontamination
10.	Placing ETT and feeding tubes through the mouth, avoiding the nasal route

VAP = ventilator-associated pneumonia; ETT = endotracheal tube.

The role for respiratory physiotherapy as a preventative strategy for VAP is unclear, with very little specific mention in the literature. Rello et al (2002a) reported that 83.3 per cent of Intensive Care Specialists utilised 'chest physiotherapy' as a non-pharmacological strategy to prevent VAP, but these authors did not explore or expand on the role, indications or rationale for respiratory physiotherapy. Ntoumenopoulos et al (2002) reported that twice daily respiratory physiotherapy comprising gravity-assisted drainage and patient positioning, chest wall vibrations, and airway suctioning (via ETT) in general medical, surgical and/or trauma patients in a tertiary ICU was independently associated with a reduction in VAP. However results from this small trial of 60 systematically allocated subjects await confirmation through a larger randomised controlled study.

Regardless of the extent and quality of the evidence for the prevention of VAP, it has been concluded that non-adherence to evidence based guidelines for the prevention of VAP is common (Cook et al. 2002; Rello et al. 2002a; Ricart et al. 2003).

2.1.8 Management

Antimicrobial therapy is the mainstay of the management of VAP and is the focus of much debate in the literature, with relatively little attention given to other, non-pharmacological components of management. It is beyond the scope of this thesis to cover the factors contributing to the selection of antibiotic treatment, such as the identification of pathological organisms, their antibiotic susceptibility, the clinical setting (e.g. duration of hospitalisation and MV, prior antibiotic use), or pharmacokinetic considerations. Similarly, considerations for prophylaxis, type, rotation and duration of antibiotic therapy will not be addressed.

Despite many advances in antimicrobial therapy, the management of patients with VAP remains difficult and complex. Because of the difficulty encountered in the diagnosis of VAP, therapy is often empirical (Chastre et al. 1995), although this may result in costly over-treatment that can be dangerous and ineffective, leading to adverse outcomes in terms of morbidity (Ioanas et al. 2003). Rapid identification of infected patients and appropriate selection of antimicrobial agents represent important clinical goals, as early targeted antimicrobial treatment of patients with VAP significantly improves outcome (Chastre & Fagon 2002; Craven et al. 2002; Ioanas et al. 2003). Worsening acute respiratory failure, septic shock, inappropriate antibiotic therapy all independently worsen the prognosis associated with VAP (Torres et al. 1990; Ioanas et al. 2004).

Management of VAP generally involves supportive care (such as MV, nutritional support, inotropic support), targeted antibiotics, and treatment of the underlying disease (Craven et al. 1997). Inappropriate therapy is related to fatality, with relative odds ratio of 5.8 (Torres et al. 1990). Significant debate continues surrounding the use of antibiotic therapy and in particular the relative merits of empiric antibiotic treatment versus single agent antibiotic therapy versus combination antibiotic therapy in the management of VAP. It is suggested that local epidemiological data combined with a patient-based approach will allow more accurate decision making regarding therapy (Rello & Diaz 2003; Valles et al. 2003). The distinction between a colonising and an infecting organism remains a difficult problem, although progress has been made in the diagnostic procedures and identification of pathogens, allowing appropriate antibiotic therapy based on documented microbiologic data (Bergogne-Berezin 1995). A recent VAP consensus conference concluded there is insufficient evidence to make strong recommendations on management decisions such as withholding empiric treatment, choosing definitive antibiotic therapy, and duration of treatment (Hubmayr 2002).

2.2 Acquired Brain Injury

One of the key concepts to emerge in the past decade is the understanding of the pathophysiology of ABI and in particular that not all neurological damage occurs at the time of the initial insult, but may evolve over the ensuing hours and days. Considerable effort is devoted to monitoring and treating patients with ABI with a view to restricting secondary or delayed insults to the injured brain at the clinical and biochemical level, thereby aiming to improve and optimise neurological outcome.

2.2.1 Definition

For the purpose of compiling statistics for the Australian Institute of Health and Welfare, Fortune and Wen (2000) reported ABI as an injury to the brain which results in deterioration in cognitive, physical, emotional or independent functioning. Acquired brain injury can occur as a result of trauma, hypoxia, infection, tumour, substance abuse, degenerative neurological disease, or stroke. These impairments to cognitive abilities or physical functioning may be either temporary or permanent, and cause partial or total disability, or

psychosocial maladjustment. Severe ABI is defined as a GCS of 3-8 after cardiopulmonary resuscitation in a patient with an abnormal computerised tomography (CT) scan of the head which reveals haematomas, contusions, oedema, or compressed basal cisterns (Stein 1996). The definitions provided in this paragraph were adopted for use in this study.

2.2.2 Incidence

It is difficult to determine the incidence of ABI as operational definitions and study methodologies can affect estimates. Fortune and Wen (2000) compiled estimates of annual ABI incidence rates that varied from 91 to 372 per 100,000 population based on international hospital data from 10 countries. The estimates of incidence of ABI in Australia range from 57 to 377 cases per 100,000 per year (Fortune & Wen 2000). Using data from Fortune and Wen (2000), and considering all the inherent concerns of definitions, methodologies used and scope of data acquisition, it is suggested a reasonable estimate of incidence rate of hospitalisation for ABI from international data is between 100 and 270 ABI cases per 100,000 per year, and for Australian data the range is between 100 and 377 ABI cases per 100,000 per year (Fortune & Wen 2000). Variance in ABI incidence rates are most likely related to definitions being developed separately for specific applications by epidemiologists, medical professionals, researchers, service providers, representative organisations and others (Fortune & Wen 2000).

It has been reported that 60 per cent of ABI in Australia occurred in people aged between 15 to 64 years and almost 70 per cent of patients with ABI were male. Males have a higher ABI incidence rate across all age groups with those aged 15 to 19 years having the highest annual incidence rate at 418 per 100,000 (Fortune & Wen 2000).

For Western Australia (WA) the standardised rate for ABI incidence was 175 per 100,000 per year, placing WA third highest nationally (after Queensland and South Australia), as compared to the national average of 149 cases per 100,000 (Fortune & Wen 2000).

2.2.3 Management

Following ABI, a sequence of destructive biochemical cascades occurs which can lead to irreversible cerebral damage (Marion 1998). Management of patients with ABI is primarily directed at manipulating and averting these cascades in order to prevent secondary brain injury (Chesnut et al. 1993; Chesnut 2004). Patients with severe ABI are critically unwell and, following basic life support measures being implemented prior to admission, they are ideally transferred as soon as possible to a trauma hospital with neurosurgery facilities (Gabriel et al. 2002; The Brain Trauma Foundation. The American Association of Neurological Surgeons. The Joint Section on Neurotrauma and Critical Care 2000b). Published guidelines for the management of severe ABI describe different therapeutic options but generally include admission to an ICU for regular intensive neurological assessment and monitoring of systemic haemodynamic variables, and interventions such as the insertion of an ICP monitor

or drain, intubation and MV, mannitol and sedation, analgesia and muscle relaxants, immobilisation in a supine or 30° head up position, and minimalisation of stimuli (Chesnut 2004; Girling 2004; Maas et al. 1997; The Brain Trauma Foundation. The American Association of Neurological Surgeons. The Joint Section on Neurotrauma and Critical Care 2000d; Yanko & Mitcho 2001). Neurosurgery for the treatment of intracranial hypertension may be necessary and may include procedures such as evacuation of mass lesions, craniectomy, or decompressive lobectomy (Chesnut 2004; Enblad et al. 2004). Outcome following ABI is drastically influenced by significant systemic hypoxia or hypotension, which can increase unfavourable outcomes threefold (Konrad et al. 1994); thus supportive measures and interventional strategies within the ICU are targeted to improve haemodynamics and oxygenation to prevent such insults (Chesnut 2004; Girling 2004; Maas et al. 1997; Myburgh 2003).

2.2.4 *Ventilator-associated pneumonia in acquired brain injury*

Ventilated patients frequently have impaired mucociliary transport, which is associated with the development of secretion retention and pneumonia (Konrad et al. 1994). Due to the depressed respiratory function, need for prolonged ventilatory support with an ETT, and post-traumatic immunosuppression, patients with severe ABI who survive their injury and initial hospitalisation are particularly vulnerable to septic episodes (Boque et al. 2000; Helling et al. 1988; Rello et al. 1992) and frequently develop pulmonary infections that may adversely affect their prognosis (Boque et al. 2000; Nadal et al. 1995). The incidence of VAP in the ABI population is reported to be as high as 83 per cent (Helling et al. 1988) although the exact frequency of VAP is unknown because of the lack of specificity of existing standard diagnostic techniques (Pingleton et al. 1992).

The ABI population, who frequently aspirate at the time of their acute injury or during the intubation process, are particularly at risk for early onset VAP (Cook et al. 1998b). The reported incidence of VAP ranges from 26 per cent for early onset VAP in ABI (Sirvent et al. 2000), to approximately 40 to 50 per cent of patients with ABI acquiring VAP at any stage during MV (Ewig et al. 1999; Helling et al. 1988; Hsieh et al. 1992), through to a reported 82 per cent VAP rate within a neurological ICU (Hilker et al. 2003). In a study of multi-trauma patients the incidence of VAP was 24 per cent, but when the presence of an ABI was considered the incidence increased to 42 per cent (Rello et al. 1992).

A VAP rate of 23 to 42 cases per 100 patients with ABI has been determined (George 1995). Furthermore, both 13 and 34 VAP cases per 1000 ventilator days in neurotrauma ICUs in the USA have been reported (A report from the NNIS System 2003; Berrouane et al. 1998). This represents a significantly higher risk adjustment rate when compared to other types of ICUs, with only patients admitted to trauma ICUs recording a higher incidence of VAP (A report from the NNIS System 2003).

Well accepted risk factors for VAP are commonly present in patients with ABI, as outlined in Section 2.1.5, including aspiration of gastric contents, ICP monitoring, duration of MV, and non-specific alterations in the respiratory defence mechanisms (Antonelli et al. 1994; Craven et al. 1986; Garrard & A'Court 1995; Torres et al. 1990). Chevret et al (1993) found the risk of VAP increased with coma, trauma, intubation or an Acute Physiological And Chronic Health Evaluation (APACHE II) score of greater than 16 on admission to ICU. VAP has also been associated with neurotrauma or a GCS of less than nine (Berrouane et al. 1998; Rello et al. 1992). Helling et al (1988) demonstrated that the severity of the ABI, as judged by the GCS, correlated with the risk of infectious complications and that the presence of coexisting chest trauma significantly increased the likelihood of subsequent pulmonary infections. In addition to the decreased conscious state and impaired airway reflexes occurring in the patient with an ABI, it has been suggested that the ABI may induce immunosuppression, that may in part explain the high risk of developing VAP (Meert et al. 1995). The first three days of admission are the time of highest risk for VAP in patients in neurosurgical ICUs (Berrouane et al. 1998), but prolonged ventilation and/or ICP monitoring significantly increase this risk, which in turn is associated with a worse outcome (Craven et al. 1986; Jimenez et al. 1989; Torres et al. 1990).

The presence of VAP in multi-trauma patients with ABI significantly increased MV and ICU length of stay but not mortality (Leone et al. 2002). The addition of a pulmonary contusion in multi-trauma patients with ABI altered gas exchange but did not appear to increase incidence of VAP, morbidity or mortality (Leone et al. 2003).

Despite the lack of standardisation and consensus with definitions and reporting mechanisms it is apparent that VAP is a significant complicating factor for many patients in ICU, and that those admitted to an ICU requiring MV following an ABI have a higher incidence of VAP than the general ICU population.

2.3 Respiratory Physiotherapy in the Intensive Care Unit

A detailed description of respiratory physiotherapy is beyond the scope of this thesis; therefore a brief synopsis only is provided. A description of individual respiratory physiotherapy treatment techniques commonly used in ICU, and their physiological rationale and evidence, is provided by Stiller (2000), Hough (2001), Pryor and Prasad (2002), Risley and Jones (2003), and Clini and Ambrosino (2004).

2.3.1 Background

Physiotherapy has been used for more than a century to improve respiratory function [Nicholson (1890) cited in Imle (1995)]. The aims of respiratory physiotherapy include prevention of respiratory complications and improvement of respiratory function in acute and chronic pulmonary disease. The precise role of the physiotherapist within the ICU may vary

but commonly may target (Risley & Jones 2003):

- Optimisation of ventilation/cardiopulmonary function
- Assistance in the weaning process, utilising ventilatory support and oxygen therapy
- Advice on positioning to optimise ventilation/perfusion matching and oxygenation
- Advice on positioning to protect joints, and to minimise potential muscle and soft tissue shortening/injury and nerve damage
- Optimisation of body position to affect muscle tone in the ABI patient
- Instigation of an early rehabilitation / mobilisation programme to assist in preventing the consequences of enforced immobility and optimise voluntary movement to promote functional independence and improve exercise tolerance.

Respiratory physiotherapy encompasses a wide variety of techniques including those to increase lung volumes, improve gas exchange, reduce the work of breathing, assist with airway clearance, and enhance mobilisation and rehabilitation. In this study, the respiratory physiotherapy interventions comprised a regimen of positioning, manual hyperinflation (MH) and airway suctioning.

2.3.1.a Positioning

In ICU, patients with ABI are generally nursed with head elevation of 30 – 45° in a neutral midline position to reduce ICP, encourage cerebrospinal fluid outflow, maximise venous drainage from the cerebral circulation, facilitate optimisation of the ventilation-perfusion ratio, improve gas exchange, and reduce risk of aspiration (Hough 2001; Myburgh 2003; Woodard & Jones 2002; Yanko & Mitcho 2001). Routine position changes for patients in ICU are undertaken, as able, to reduce the adverse effects of restricted mobility such as contractures or pressure areas. From a respiratory physiotherapy perspective, positioning is considered an integral part of treatment and a primary intervention in its own right, although generally it is combined with other techniques (Hough 2001). Positioning by physiotherapists can be used with the physiologic aims of optimising oxygen transport through its effects of improving ventilation/perfusion matching, increasing lung volumes, reducing work of breathing, minimising the work of the heart, and enhancing mucociliary clearance (Clini & Ambrosino 2004; Risley & Jones 2003; Stiller 2000). Specific examples of positioning that may be incorporated into the respiratory physiotherapy management of patients in ICU include, but are not limited to, sitting upright to improve lung volumes and side lying with the affected side uppermost to improve ventilation and/or use of specific gravity assisted drainage positions (GADP) to assist with clearance of airway secretions. Dean (1994; 2002) provides a detailed description of the physiological and scientific rationale for the use of positioning as part of respiratory physiotherapy to improve oxygen transport in patients with acute cardiopulmonary dysfunction.

2.3.1.b Manual hyperinflation

The technique of manual hyperinflation (MH), as performed by physiotherapists, was first

described by Clement and Hubsch (1968), and is also referred to as 'bag squeezing' or 'bagging'. Manual hyperinflation involves disconnecting a patient from a ventilator and then delivering a volume of gas via a manual resuscitation circuit (approximately 150% of tidal volume) to inflate the patient's lungs. Use of MH by physiotherapists is common in the treatment of intubated patients with the aim of increasing alveolar oxygenation, reversing atelectasis, or mobilising pulmonary secretions (Denehy 1999; Hodgson et al. 1999; Jones et al. 1992b; King & Morrell 1992). The usual MH technique involves a long inspiration with an inspiratory pause, to assist collateral ventilation and stabilisation of alveoli, and a short expiration in order to maximise mean expiratory flow to enhance secretion clearance (Paratz 1992; Stiller 2000). Several authors have provided descriptions of MH, as performed by physiotherapists (McCarren & Chow 1996; McCarren & Chow 1998; Patman et al. 2001; Maxwell & Ellis 2002), whilst mechanisms for sputum clearance via MH have been detailed by Maxwell and Ellis (1998). The influence of circuit type, circuit compression and rapid release on expiratory flow during MH have been investigated (Maxwell & Ellis 2003; Maxwell & Ellis 2004) in an attempt to document current MH practice as compared to desired optimal, albeit theoretical, technique performance.

Evidence supports the use of MH to improve oxygenation (Jones et al. 1992b; Patman et al. 2000; Stiller et al. 1996), re-expand acute atelectasis (Stiller et al. 1990; Stiller et al. 1996), enhance sputum clearance (Denehy 1999; Hodgson et al. 2000), and to improve static lung compliance (Berney & Denehy 2002; Berney et al. 2004; Jones et al. 1992b; Hodgson et al. 2000; Patman et al. 2000). There are also potential complications associated with the use of MH. Cardiovascular and haemodynamic instability (Enright 1992; Paratz 1992; Singer et al. 1994; Stone et al. 1989; Stone et al. 1991a; Stone et al. 1991b), risk of barotrauma, volutrauma and pneumothorax (Clarke et al. 1999; Dreyfuss et al. 1985; Dreyfuss et al. 1988; Haake et al. 1987), and temporary increases in ICP in patients with ABI (Crosby & Parsons 1992; Ersson et al. 1990; Garradd & Bullock 1986; Paratz & Burns 1993) have all been reported during physiotherapy interventions involving MH. However, there are no studies that have specifically evaluated the effect of MH on VAP. Similarly, the clinical significance of changes arising during respiratory physiotherapy in intracranial and haemodynamic variables in patients with ABI on patient outcomes has not been investigated.

2.3.1.c Suctioning

Suctioning via an ETT or tracheostomy aims to stimulate a cough and remove secretions from the airways and is commonly performed in ICU patients by nurses and physiotherapists due to inability of the patient to cough effectively, presence of sputum plugging or to assess the patency of the artificial airway. The efficacy of suctioning has not specifically been investigated and established (Clini & Ambrosino 2004); although anecdotally within the clinical setting suctioning does stimulate a cough and assist with airway clearance in the majority of intubated patients in which it is performed. In particular, the effectiveness of

suctioning in terms of sputum yield, optimal technique, indications and frequency of performance, improvements in patient outcomes, and cost effectiveness has not been established. Suctioning is a technique that is frequently incorporated into a regimen of respiratory physiotherapy, but the effect of suctioning as performed in isolation by physiotherapists has not been investigated.

Literature to date on suctioning has primarily focussed on short term physiological responses to suctioning and subsequent avoidance or management of potential hazards. Tracheal trauma, suctioning induced hypoxemia, hypertension, cardiac arrhythmias, VAP, anxiety and pain have all been associated with the suctioning procedure (Thompson 2000). As it is also well established that suctioning increases ICP and blood pressure in patients with ABI (Brucia & Rudy 1996; Ersson et al. 1990; Imle et al. 1997; Kerr et al. 1996; Kerr et al. 1997; Kerr et al. 1999; Parsons & Shogan 1984; Rudy 1991), it is recommended that use of suctioning is minimised and should be preceded by adequate sedation and analgesia, accompanied by 100 per cent hyper-oxygenation and hyperinflation, and limited to two suctioning attempts per procedure (Bader & Palmer 2000; Brooks et al. 2001; Ersson et al. 1990; Kerr et al. 1993; Thompson 2000; Wainwright & Gould 1996).

Nurses are reported as commonly using normal saline installation as part of their routine suctioning intervention to assist secretion removal in intubated patients (Ackerman et al. 1996; Gallon 1992; Schwenker et al. 1998; Thompson 2000). However, due to potential adverse effects on oxygen saturation and cardiovascular stability, and the lack of reported consensus for increase in sputum yield, the use of normal saline instillation is not supported by the literature (Ackerman et al. 1996; Blackwood 1999; Brooks et al. 2001; Thompson 2000), even in the presence of pulmonary infection (Ackerman & Mick 1998). Also, normal saline instillation has been demonstrated to dislodge significant numbers of viable bacterial colonies from the ETT into the lower airway, which may contribute to lower airway colonisation and VAP (Hagler & Traver 1994). Normal saline instillation is not part of the routine suctioning technique followed by physiotherapists at RPH.

There is insufficient evidence as to whether suctioning should be performed with a clean or sterile technique (Brooks et al. 2001; Thompson 2000). At the RPH ICU, suctioning of the airway involves a clean technique performed with a single use sterile-sleeved catheter and the use of a new set of clean gloves for each suction pass.

In-line closed suctioning systems are significantly less efficient than open system suctioning (Lindgren et al. 2004) and are associated with increased colonisation of the ventilator tubing with multi drug-resistant micro-organisms (Topeli et al. 2004). Use of in-line closed suctioning systems does not result in decreased incidence of VAP (American Association of Respiratory Care 2003; Brooks et al. 2001; Dodek et al. 2004; Lorente et al. 2005; Topeli et al. 2004), duration of MV, length of ICU stay or mortality (Lorente et al. 2005; Topeli et al. 2004). Patient cost per day for in-line closed suction is more expensive than open suction

systems (Lorente et al. 2005). Currently a systematic review is being undertaken to investigate the efficacy of closed tracheal suctioning systems versus open tracheal systems for mechanically ventilated adult patients (Subirana et al. 2004).

Clinical practice guidelines for the suctioning procedure have been published (American Association of Respiratory Care 1993; Brooks et al. 2001). These guidelines form the basis for the suctioning technique performed by physiotherapists at RPH, with the exception that use of hyperventilation or normal saline, are not part of the standard suctioning procedure in the ICU at RPH.

2.3.1.d Other respiratory physiotherapy techniques

In addition to the techniques of positioning, MH and airway suction, physiotherapists in ICU have a number of other manual techniques available to facilitate airway clearance in patients receiving MV.

Percussion

Percussion, or chest clapping, is defined as "...a downward force rhythmically applied by the physiotherapist's cupped hands to the patient's thorax over the involved lung segment(s)." (Starr 1992, pp 101) with the aim of loosening secretions from the airway walls (Hough 2001; Pryor 1992). Percussion creates an energy wave that is transmitted through the chest wall causing vibrations within the underlying lung tissue, enhancing mucociliary clearance from that lung segment (Starr 1992). The reported rate of percussion performed by physiotherapists on adult patients has ranged from 0.1 to 8.0 Hertz (Blazey et al. 1998; Starr 1992; Gallon 1991), and a mean force of 58.1 Newtons has been measured from manual chest percussion (Blazey et al. 1998). Percussion is indicated in the presence of excessive sputum production or retention, and is usually combined with GADP, forced expiratory techniques, and vibrations or shaking to increase the probability of secretion removal (Gallon 1991; Gallon 1992; Starr 1992). However specific evidence based guidelines for the required application and performance of the percussion technique are lacking.

The majority of the literature on percussion involves non-intubated patients who have chronic excessive sputum production, and rarely investigates the percussion technique in isolation, but rather as part of a regimen of respiratory physiotherapy. In a review of physiotherapy for airway clearance in adults, it was concluded that despite there being a physiological rationale and place for the use of percussion, the clinical evidence for its use was inconclusive (Pryor 1999). Recently it has been concluded that there is not enough evidence to support or refute the use of respiratory physiotherapy involving a regimen including GADP, percussion, chest wall vibrations and shaking in people with chronic obstructive pulmonary disease and bronchiectasis (Jones & Rowe 2004). In patients with cystic fibrosis airway clearance techniques (including GADP, percussion, vibration and shaking) have short-term beneficial effects in improving mucus clearance, however it remains to be

determined whether a specific type of treatment is more beneficial over others (Thomas et al. 1995; van der Schans et al. 2004). There was no evidence to draw conclusions concerning any long-term effects, or to support claims of airway clearance techniques, including percussion, being harmful in patients with cystic fibrosis (van der Schans et al. 2004).

In the intubated ICU population the effectiveness of percussion used in isolation has not been investigated (Stiller 2000). In five patients with acute lung atelectasis the effects of percussion as part of a regimen of respiratory physiotherapy including GADP and vibrations were investigated, with an anecdotal finding that percussion of these critically ill patients increased cardiac arrhythmias and was an indication of poor tolerance to the treatment (Hammon & Martin 1981). Specific details as to whether the respiratory physiotherapy interventions were standardised, or whether techniques such as MH or suction were utilised is not provided, limiting further interpretation of this study by Hammon and Martin (1981). A regimen of respiratory physiotherapy involving GADP, percussion, vibrations and suction in 20 patients in ICU reduced static total lung compliance (for at least two hours) but not oxygenation in those with clear lungs, but resulted in no changes in lung compliance or oxygenation in the patients with lung pathology (Jones et al. 1992b). In ICU, use of GAPD and percussion for up to 15 minutes has been shown to increase metabolic costs in the short-term. In surgical patients an increase in oxygen consumption of up to 40 per cent has been reported (Horiuchi et al. 1997), whilst in those with acute lung injury an increased oxygen consumption of 22 per cent was recorded (Davis et al. 2001). The link between these acute physiological changes and patient outcomes remains to be determined. In those with more than 40 millilitres of sputum per day, GAPD and percussion increased sputum volume significantly (Davis et al. 2001). Historically based on anecdotal clinical experience the use of percussion in those with ABI was considered contra-indicated as it may lead to elevations in ICP. However, use of percussion alone in adult patients with ABI has not been associated with significant increases in ICP (Brimioulle et al. 1988; Brimioulle et al. 1997; Paratz & Burns 1993).

In summary, percussion has been shown facilitate airway clearance in stable patients with chronic excessive secretions, but does not assist airway clearance in those who have minimal secretions, and may be detrimental in patients with no apparent pulmonary disorder. Due to the inconclusive nature as to the effectiveness of percussion in patients receiving MV, it was deemed unnecessary and potentially inappropriate to include this technique as part of the respiratory physiotherapy treatment regimen used in this study involving intubated adult patients in ICU.

Vibration

Chest wall vibrations are the "...isometric co-contraction of the physiotherapist's upper extremities, producing a vibration that is transmitted from the physiotherapist's hands to the patient's thorax during expiration." (Starr 1992, pp 109). Vibration is performed by placing the

flat of the hands over the chest wall of the affected lung area and vibrating the hands quickly (Pierce 1995). These vibratory actions, or fine oscillations, of the hands are directed inwards against the chest in the direction of normal movement of the ribs and performed on exhalation after a deep inspiration (Hough 2001; Pryor et al. 2002). The vibration is superficial and creates an oscillatory movement that is reflected to the deep tissues, thereby augmenting expiratory airflow, mobilising mucus and promoting its flow (Pierce 1995; Pryor 1992). Shaking is a coarser movement in which the chest wall is rhythmically compressed throughout expiration (Hough 2001; Pryor et al. 2002; Starr 1992). Vibrations and shaking are techniques that represent both ends of a spectrum of external compression to the chest wall during expiration. The physiotherapist uses their discretion in determining the amplitude and amount of compressive force used during the technique that they find the most clinically useful (Pryor et al. 2002; Starr 1992). Empirically physiotherapists use vibration and shaking together with GADP and percussion to augment expiratory flow and to enhance mucociliary clearance.

The use of vibrations by physiotherapists is common (Brooks et al. 2003; McCarren et al. 2003) but there is very limited research in adults investigating the performance or effectiveness of vibrations and/or shaking in isolation. Most studies investigating vibrations or shaking have included these techniques as part of a respiratory physiotherapy regimen, commonly in association with GADP and percussion. The study population has mostly comprised non-intubated patients with excessive secretion production.

The effectiveness of vibrations in the ICU patient population has not been established, with very little known about the effect of vibration on airway clearance (McCarren et al. 2003; Stiller 2000). Chest wall compressions, in addition to MH, significantly increased the mean expiratory flow rate over and above MH alone in the intubated patient (MacLean et al. 1989), which may be one of the mechanisms for promoting airway clearance. Currently what is reported is that the addition of vibrations into a regimen of respiratory physiotherapy of MH and suction failed to improve lung compliance or oxygenation in patients following cardiac surgery (Eales et al. 1995) or improve the resolution of lobar atelectasis (Stiller et al. 1996). There is a need for further study to examine the effects of vibration or shaking on airway clearance in the ICU patient population, and to establish guidelines on frequency, intensity, duration and appropriate patient populations for the use of these techniques. Also the cumulative effect of vibration and shaking as part of a regimen of respiratory physiotherapy warrants further investigation.

Due to the inconclusive nature as to the effectiveness of vibration and shaking, it was deemed unnecessary and potentially inappropriate to include these manual techniques as part of the respiratory physiotherapy treatment regimen used in this study involving intubated adult patients in ICU.

2.3.2 Service provision

The provision of physiotherapy services to ICUs has long been considered an essential and integral part of the management of patients in ICU. In their recommendations for services, personnel and standards for delivery of care in a critical care setting, the Task Force on Guidelines of the Society of Critical Care Medicine (Task Force on Guidelines of the Society of Critical Care Medicine 1988; Task Force on Guidelines of the Society of Critical Care Medicine 1991) stated that 24-hour availability of chest physiotherapy is a minimum requirement for an ICU. Similarly, Ferdinande and Members of the Task Force of the European Society of Intensive Care Medicine (1997) recommended that one dedicated physiotherapist per 12 ICU beds is an essential minimum requirement. Many others also have advocated the need for 24-hour access to physiotherapy services in the ICU (Ciesla 1996; Intensive Care Society 1983; Mackenzie et al. 1989; Oh 2003; Paterson 1997).

In Australia, previous reviews indicate large variation in the provision of respiratory physiotherapy services between major hospitals. Ntoumenopoulos and Greenwood (1991) reported that 45 per cent of Australian hospitals provided some kind of 24-hour physiotherapy coverage but only seven per cent had rostered night shifts. Jones, Hutchinson and Oh (1992) reported that a 24-hour, on-call service was available in only 49 per cent of ICUs in Australia, compared to 97 per cent in the UK, and 41 per cent of Australian ICUs were provided with some form of rostered after-hours service, compared to 16 per cent in the UK. From a survey of Australian and New Zealand hospitals in which coronary artery surgery was performed, Tucker et al (1996) reported that 57 per cent of hospitals had an on-call physiotherapist available for after hours care and only one hospital routinely provided an overnight service. The most recently published data on current levels of respiratory physiotherapy services provided within Australia reports almost 90 per cent of ICUs had physiotherapy available during the week but over 25 per cent had on-call service only on weekends and less than 10 per cent had weekday or weekend evening physiotherapy coverage (Chaboyer et al. 2004).

There is, additionally, no consensus as to the extent of the coverage required, with the hours of physiotherapy services varying considerably between ICUs. In some, including RPH, 24-hour a day, 7-days a week rostered physiotherapy is provided, whilst in others physiotherapy is provided only during a part of the day.

There is currently no evidence from which to determine the optimal level of physiotherapy services to the ICU and whether increased levels of service result in improved patient outcomes and cost savings. Stiller (2000) noted that despite the widespread use of physiotherapy for intubated, mechanically ventilated patients in ICU, there is little research to support its role. When discussing the current dilemmas and future challenges for respiratory pulmonary physiotherapy in Australia, Jenkins (1997, p4), suggests that "Also urgently needed is evidence that such interventions are cost effective, for example by reducing

mortality and morbidity, and enabling earlier discharge from intensive care and/or hospital." For respiratory physiotherapists "It is essential to provide and market outcome data showing benefit."(Jenkins 1997). Similarly Culham (1998, p65) stated "Our credibility and survival as a health care profession are at risk if we are unable to demonstrate that our treatment approaches have a significant effect on the health of our clients and are cost effective.".

2.3.3 Role in ventilator-associated pneumonia

The main goals of respiratory physiotherapy include promotion of effective alveolar ventilation and adequate oxygenation, clearance of airway secretions, maintenance of chest wall mobility, and enhancement of exercise tolerance and mobility (Brooks et al. 2003). Respiratory physiotherapy interventions, including techniques such as positioning, MH, endotracheal suctioning and chest wall manoeuvres (such as percussion, shaking and vibrations) may be beneficial in reversing or preventing ventilation – perfusion mismatching, impaired airway clearance, immobility and other possible secondary complications of ABI, thereby improving patient outcomes. The use of prophylactic respiratory physiotherapy in patients following trauma and/or ABI is advocated to prevent complications such as VAP (Boughton & Ciesla 1986; Ciesla 1994; Imle 1995), although these recommendations are based on opinions as opposed to documented evidence. Improved patient outcomes may also be of economic benefit to the ICU. Ciesla (1996) hypothesised that respiratory physiotherapy may reduce the incidence of pulmonary infections, improve pulmonary function, and may decrease the duration of MV, prevent the need for tracheostomy with the benefits of reduced costs and shorter hospital stay. However, it has also been reported that respiratory physiotherapy may cause marked temporary changes in intracranial and haemodynamic variables in patients with ABI (Ciesla 1996; Ersson et al. 1990; Garradd & Bullock 1986; Imle et al. 1997; Paratz 1992; Paratz & Burns 1993). The clinical significance of these changes on patient outcomes has not been investigated.

It has been suggested that the use of respiratory physiotherapy and early ambulation are strategies to modify risk factors and prevent VAP (Craven et al. 1997; Craven et al. 1998; Rello et al. 2002a). The role of respiratory physiotherapy to loosen and drain pulmonary secretions in addition to turning and positioning every two hours in order to prevent pneumonia is recommended as part of the acute care management of patients with severe ABI (Yanko & Mitcho 2001), although these authors did not specify which techniques of respiratory physiotherapy should be utilised. In a study investigating risk factors for VAP in critically ill trauma patients, Harris et al (2000) reported that 42.5 per cent of patients received respiratory physiotherapy, and those with VAP were significantly more likely to have received respiratory physiotherapy than those without VAP (57.8% vs. 39.3%, $p = 0.02$). Specific details of the techniques and duration of respiratory physiotherapy utilised were not described and it was concluded that further research to evaluate early implementation and optimal frequency of respiratory physiotherapy in preventing VAP was warranted (Harris et

al. 2000). In a survey of Intensive Care Specialists, 83.3 per cent utilised respiratory physiotherapy as a non-pharmacological strategy to prevent VAP based on grade A evidence (supported by two randomised control trials). A further 8.3 per cent of Intensive Care Specialists reported that respiratory physiotherapy services were unavailable, 1.7 per cent referred to financial constraints and 1.7 per cent cited 'nurse convenience' for not utilising physiotherapy, whilst 3.3 per cent of Intensive Care Specialists disagreed with the evidence recommending respiratory physiotherapy as a non-pharmacological strategy to prevent VAP (Rello et al. 2002a).

2.3.4 *Effectiveness of respiratory physiotherapy in the intensive care unit*

Evaluation of the effectiveness of respiratory physiotherapy in the ICU is limited by a lack of reliable, valid, and appropriate outcome measures that are responsive to change and that reflect the goals of respiratory physiotherapy, and many questions remain about the effectiveness of respiratory physiotherapy in the management of acute medical conditions such as pneumonia, atelectasis, pleural effusion and pneumothorax (Crowe et al. 2003). There is limited research on respiratory physiotherapy in the ICU (Stiller 2000), particularly related to VAP.

In a study of 10 patients with atelectasis or pneumonia, respiratory physiotherapy involving a single 30-minute session of chest wall vibrations and tracheal suction improved oxygenation (Holody & Goldberg 1981). Changes in ICP during positioning and percussion were studied in 32 patients with severe acute neurological dysfunction by Brimioulle et al (1988), with the finding that ICP was not significantly affected by percussion but increased markedly during patient positioning. In a study of 16 patients with severe head injury and pulmonary complications, Imle and colleagues (1988) investigated the influence of GADP either head down or head flat, in conjunction with percussion, vibration and suctioning, on ICP and cerebral perfusion pressure (CPP). Measures taken during the 15 minute treatment showed significant increases in ICP (with larger increases in the head down position) but no significant changes in CPP. No significant changes in heart rate (HR), mean arterial pressure (MAP), ICP or CPP between measures before and 10 minutes after respiratory physiotherapy were reported (Imle et al. 1988).

Ntoumenopoulos et al (1998) investigated the use of respiratory physiotherapy involving twice-daily 20-minute treatments of MH and GADP in 46 trauma patients receiving MV for greater than 24 hours. Compared to subjects randomised to a control group receiving routine nursing care (including regular turning and tracheal suctioning, but not MH or GADP), Ntoumenopoulos et al (1998) found no significant alteration in the duration of MV, length of stay in ICU, pulmonary function or mortality associated with the addition of respiratory physiotherapy. Twice as many subjects were withdrawn from the control group (8/24) due to a suspicion of VAP; of these eight, four developed VAP based on clinical criteria whilst four

had a clinical suspicion of VAP. Three of the four subjects withdrawn from the treatment group went on to satisfy clinical criteria for VAP; however this difference between groups was not statistically significant, suggesting no change to the incidence of VAP resulted from the addition of respiratory physiotherapy to routine nursing care. However, Ntoumenopoulos et al (1998) acknowledged that clinical judgement and the non-specific clinical criteria used in their study did not provide an accurate diagnosis of VAP. Future study with consideration of power and sample size determination, use of standard clinical criteria (such as the CPIS) for the diagnosis for VAP, and standardised respiratory physiotherapy management strategies that are continued for the entire duration of ICU stay, were advocated (Ntoumenopoulos et al. 1998).

In a convenience sample of 19 subjects it was found that a single 20-minute respiratory physiotherapy intervention, consisting of GADP (side-lying), MH and tracheal suctioning, significantly improved lung compliance and amount of sputum cleared in patients requiring MV with hypoxia and lung collapse and/or consolidation but not necessarily a diagnosis of VAP (Hodgson et al. 2000). A single respiratory physiotherapy treatment of GADP, MH and airway suction to 17 patients in ICU with acute lung injury did not significantly improve oxygenation or pulmonary compliance (Barker & Adams 2002). This study by Barker and Adams (2002) did not aim to measure long term outcomes or effects of the respiratory physiotherapy, but rather to quantify the potential for lung de-recruitment that patients with acute lung injury may experience following physiotherapy. A meta-analysis (involving 18 trials) of the effectiveness of respiratory physiotherapy in ICU found that respiratory physiotherapy was useful in the prevention and resolution of atelectasis and the prevention of post-operative pulmonary complications, but not in the improvement of blood oxygenation or the prevention of pneumonia (Devroey et al. 2002).

A recent study of 60 adults receiving MV for greater than 48 hours in a combined medical, surgical and trauma ICU, compared an intervention group which received twice daily respiratory physiotherapy comprising GADP for at least 20 minutes, four sets of six cycles of expiratory chest wall vibrations, and airway suctioning (via ETT or tracheostomy tube, at least three times), to a control group (Ntoumenopoulos et al. 2002). In this study, MH was not included in the respiratory physiotherapy regimen provided to the 24 subjects allocated to the intervention group, and all subjects received routine re-positioning and airway suctioning by nursing staff as required. For the purpose of their study, VAP was defined using both clinical criteria and a modified CPIS. The addition of respiratory physiotherapy to routine nursing care was independently associated with a significant reduction in VAP (39% in the control group versus 8% in the treatment group, $p=0.02$), but there were no significant differences in duration of MV, length of ICU stay or mortality (Ntoumenopoulos et al. 2002).

In contrast, no significant difference in the incidence of VAP or timing of onset of VAP following twice daily respiratory physiotherapy involving GAPD and forced expiratory

techniques in a study of 22 subjects receiving MV for greater than 48 hours in a general ICU has been reported (Norrenberg et al. 2004). However the findings of Devroey et al (2002) and Norrenberg et al (2004) are only presented in an abstract and thus further exploration of the respiratory physiotherapy techniques studied and critique of the results obtained is not possible.

On the basis of available evidence, Crowe et al (2003) and Dodek and colleagues (2004) were unable to make a recommendation regarding the use of respiratory physiotherapy as part of their evidence-based clinical practice guideline for the prevention of VAP.

To date there is no research concerning the effectiveness of respiratory physiotherapy in preventing or treating the pulmonary conditions for the ABI population. Hence from an evidence-based perspective there is no justification for the role of respiratory physiotherapy in ICU for patients with ABI.

2.4 Summary

"Regardless how common it is, and despite voluminous literature already in existence, controversies remain in every aspect of VAP including epidemiology, diagnosis, treatment, prevention, and outcome assessment." (Chinsky 2002.p1883). Accurate data on the epidemiology of VAP are limited by the lack of standardised criteria and definitions for its diagnosis, but despite the lack of standardisation and consensus with definitions and reporting mechanisms it is apparent that VAP is a significant complicating factor for many patients in ICU. Ventilated-associated pneumonia is associated with prolonged length of stay, increased hospital mortality rates and may substantially increase the cost of hospitalisation two to three-fold by lengthening the duration of MV, time in ICU, and overall hospital stay. To date, few interventions, including respiratory physiotherapy, have been shown to be beneficial in the prevention of VAP.

Patients with severe ABI are commonly admitted to the ICU and considered to be at a high risk for developing respiratory complications such as VAP, which could potentially impact on the ICU costs and outcomes.

Respiratory physiotherapy encompasses a wide variety of techniques including those to increase lung volumes, improve gas exchange, and assist with airway clearance. Studies of respiratory physiotherapy are limited in number, often describe the treatment regimen inadequately, investigate various non-standardised combinations of techniques, and are generally poorly powered; this is especially evident in studies of ICU patients and respiratory physiotherapy. Evidence supporting the use of respiratory physiotherapy techniques has historically arisen from studies of stable extubated patients who regularly produce chronic excessive amounts of sputum, limiting the ability to generalise findings to the intubated patient in ICU.

Respiratory physiotherapy may be provided to prevent and/or treat VAP in patients with ABI,

with the theoretical rationale that respiratory physiotherapy to improve airway clearance and enhance gas exchange may reduce the incidence of pulmonary infections and thus VAP, and may decrease the duration of MV, prevent the need for tracheostomy and hence result in reduced costs and shorter hospital stay. Although respiratory physiotherapy for patients with ABI may be beneficial in reversing or preventing VAP, to date there are no data concerning the effectiveness of respiratory physiotherapy in patients with ABI. Hence from an evidence-based perspective, at present there is no justification for the role of respiratory physiotherapy in the management of patients with ABI in the ICU.

Chapter 3 Research Method

This chapter provides an overview of the research methodology, and describes the aims, study design, hypotheses, study population, sample size determination, and the independent and dependent variables. A description of the procedures for data collection, ethical considerations and the methods of data analysis are also provided.

3.1 Study Design and Aims

A two-part, prospective randomised controlled trial was undertaken to investigate the effects of respiratory physiotherapy on the incidence and resolution of VAP in patients admitted with ABI to the ICU at RPH (see Figure 3.1 for schematic view).

The aim of Part A of the study was to establish if the provision of regular prophylactic respiratory physiotherapy interventions, in addition to routine medical and nursing care, influenced the incidence of VAP. In Part A subjects were randomised (Section 3.5.1) to one of the following two groups:

Treatment Group 1: 24-hour respiratory physiotherapy service (six interventions: approximately every four hours throughout the day and night) in addition to routine medical and nursing care and daily passive movements,

Control Group 2: no respiratory physiotherapy service – routine medical and nursing care and daily passive movements only.

The aim of Part B of the study was to establish if the provision of a regimen of regular respiratory physiotherapy, in addition to routine medical and nursing care, influenced the progression and/or resolution of VAP.

Subjects from Part A who developed VAP, based on criteria as outlined in 3.4.2 Dependent variables, were transferred to Part B of the study and re-randomised to either:

Treatment Group 3: 24-hour respiratory physiotherapy service (six interventions: approximately every four hours throughout the day and night) in addition to routine medical and nursing care and daily passive movements,

Control Group 4: no respiratory physiotherapy service – routine medical and nursing care and daily passive movements only.

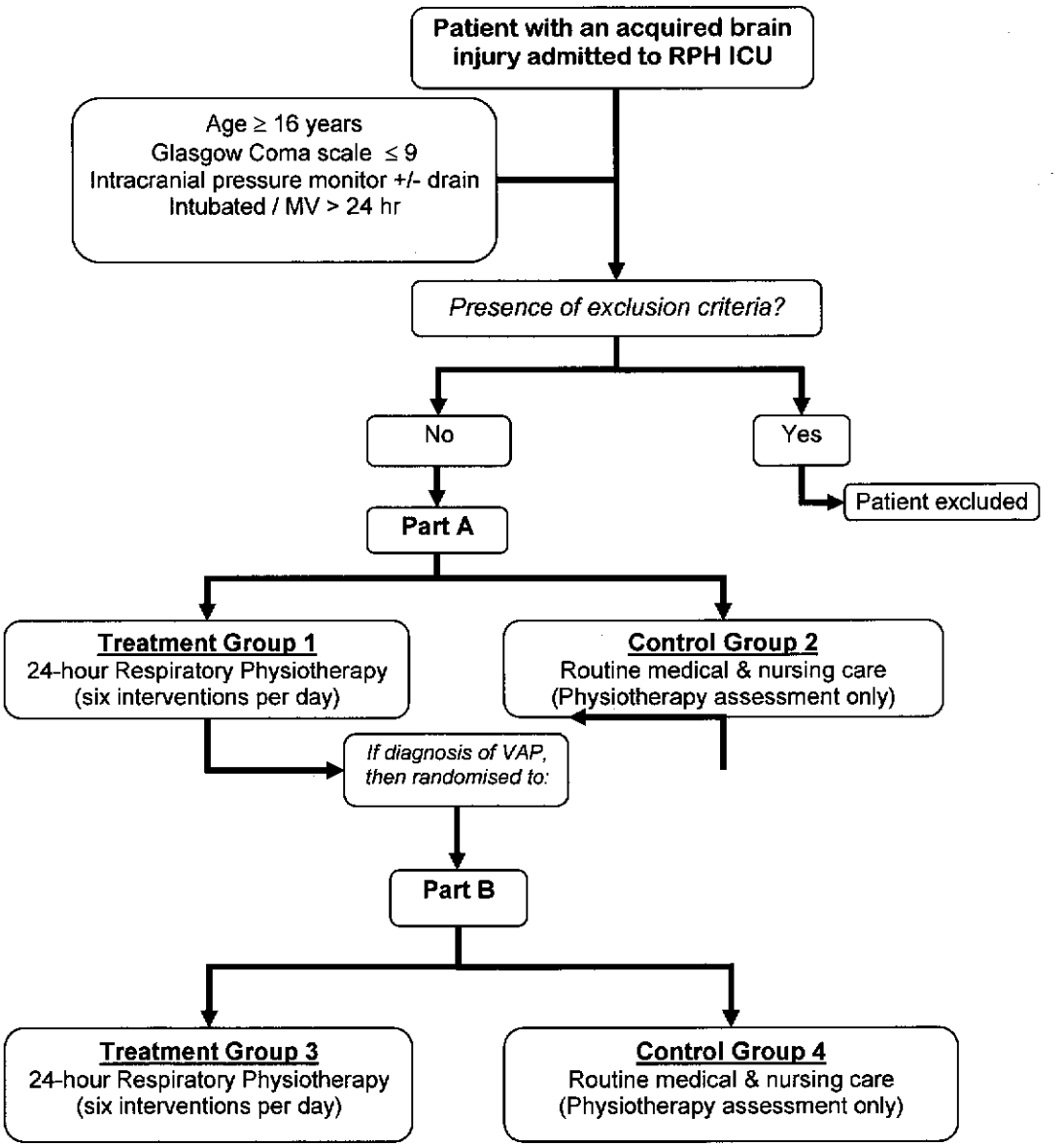

Figure 3.1 Flow diagram illustrating the study design

3.2 Research Hypotheses

The following hypotheses were proposed based on a review of the literature:

H_1: the provision of prophylactic respiratory physiotherapy, in addition to routine medical and nursing care, to the ABI patient population in the ICU significantly decreases the incidence of VAP.

H_2: the provision of respiratory physiotherapy, in addition to routine medical and nursing care, to the ABI patient with VAP in the ICU significantly assists in the resolution of VAP.

H_3: the level of respiratory physiotherapy service provided in the ICU significantly influences ABI patient outcomes, such as duration of MV and length of ICU stay.

H_4: the provision of respiratory physiotherapy to patients with ABI in the ICU is cost effective in decreasing the incidence of MV, duration of MV and length of ICU stay.

3.3 Subjects

Patients admitted to the ICU at RPH following an ABI who satisfied the inclusion criteria were eligible for participation in the study.

3.3.1 Inclusion criteria

Inclusion criteria comprised meeting all of the following:

- Aged 16 years or older
- GCS less than or equal to (≤) nine on admission to the ICU
- Presence of an ICP monitor or drain
- Invasive mechanical ventilatory support for greater than (>) 24 hours

Eligible subjects were prospectively randomised to a study group on admission to the ICU.

3.3.2 Exclusion criteria

Exclusion criteria comprised at least one of the following:

- Patients not for active therapy
- Patients with excessive respiratory support requirements, defined as:
  - nitric oxide ventilation,
  - fraction of inspired oxygen [FiO_2] > 0.8,
  - and/or positive end expiratory pressure [PEEP] > 10 centimetres of water [cmH_2O].

  Patients with any of these criteria would not receive MH, as per RPH ICU standard operating policy, and may have limited positioning and airway suctioning due to concerns regarding excessive oxygen consumption. Therefore the application of a regular physiotherapy intervention, as per Groups 1 or 3, would not be possible.

- Patients with unstable haemodynamic status, defined as:
  - MAP [in millimetres of Mercury (mmHg)] > 120 or < 60,
  - and/or HR (in beats per minute) > 120 or < 60,
  - labile MAP or HR,
  - presence of new cardiac arrhythmias requiring definitive intervention,
  - excessive inotropic support requirements i.e. noradrenaline or adrenaline infusion at > 30 milligrams per hour.

  These MAP and HR criteria are based on greater than 10 per cent variation from the normal range (Morgan 2003). Adequacy of tissue perfusion and cerebral oxygenation may be a concern, particularly in the ABI population, if significant variation from the normal range exists. The dosage of vasoactive drugs listed, allowing for a range of titration based on body weight and clinical effect, result from an arbitrary exclusion level based on the author's clinical experience.

- Patients with unstable neurological status, defined as:
  - labile ICP or CPP,
  - sustained ICP > 25mmHg,
  - sustained CPP < 70mmHg.

  The primary focus of ICU management of patients with ABI is to prevent secondary brain insult characterised by a reduction in cerebral substrate utilisation, particularly oxygen, arising from hypotension and hypoxia (Myburgh 2003). The above neurological criteria are from the Brain Trauma Foundation management guidelines (The Brain Trauma Foundation. The American Association of Neurological Surgeons. The Joint Section on Neurotrauma and Critical Care 2000a; The Brain Trauma Foundation. The American Association of Neurological Surgeons. The Joint Section on Neurotrauma and Critical Care 2000c). Patients with any of these criteria would not receive any physiotherapy, and basic nursing care including positioning and airway suctioning would be minimised, as per RPH ICU standard operating procedures, until definitive intervention had resulted in a stable neurological status. Therefore the application of a regular physiotherapy intervention, as per Groups 1 or 3, would not be possible.

For the purpose of this study 'labile' was considered as a clinically significant alteration in any of: MAP, HR, ICP, or CPP of 20 per cent or more of resting values, occurring spontaneously without stimulation, which necessitated definitive intervention. This definition is supported by MacIntyre (2001) who described an acute increase or decrease in blood pressure, in the order of at least 20 per cent, being indicative of haemodynamic instability.

3.3.3 Withdrawal criteria

In the event that a subject subsequently did not require ventilatory support for greater than 24 hours, and therefore did not fulfil all the inclusion criteria, the subject was withdrawn from the study.

Subjects with major lobar collapse or collapse of one lung failing to respond to other measures such as positioning and nursing care after one hour were withdrawn from the study and received respiratory physiotherapy, as this group of patients has been shown to benefit from physiotherapy (Fourrier et al. 1994; Stiller et al. 1996).

Patients who, after initial inclusion in the study, developed any of the exclusion criteria (Section 3.3.2) that were sustained for a period of 12 hours or more, such as neurological instability, were withdrawn. Transient changes in medical status (such as short-term alterations in respiratory, neurological or cardiovascular status following positioning or nursing and medical procedures) or subject unavailability due to procedures (such as CT scans, replacement of ICP monitoring devices, central line insertion or percutaneous tracheostomy) may have resulted in a physiotherapy treatment session being missed, but did not trigger subject withdrawal until three consecutive scheduled treatments were missed.

In Part A and B any subject receiving respiratory physiotherapy services outside of those provided by group randomisation was withdrawn from the study. With the exception of those in whom active management was ceased, any subject withdrawn from the Control Groups (i.e. Groups 2 or 4) through the actions of the Intensive Care Specialist or treating physiotherapist received the same respiratory physiotherapy interventions as the Treatment Groups (i.e. Groups 1 or 3). Data collection was continued, with these subjects not receiving their allocated intervention being retained in the study but treated as a 'non- complier'. This ensured that full data from subjects not receiving their allocated intervention were collected and intention to treat analysis was not undermined.

3.3.4 Sample size

3.3.4.a Part A

It was not possible to directly estimate effect size for this study due to the lack of published data as to the effectiveness of respiratory physiotherapy for the ABI population. For the purpose of sample size determination, it was determined that this study would have a power of 80 per cent to show that the incidence of VAP for the Treatment Group was not the same (either lower or higher) as the incidence of VAP for the Control Group. It was assumed that the incidence of VAP for the Control Group population would be precisely 30 per cent, and that an absolute difference of 20 percentage points or more is clinically important. This resulted in a sample size in the two groups of 65 each, with an alpha level (2 tailed) set at 0.05 (PowerAndPrecision™ Release 2.0, 2000). Allowing for a withdrawal rate of 10 per cent, sample size for Part A was therefore determined to be 72 subjects per group.

Prior to commencing this study the number of patients admitted to the ICU at RPH likely to satisfy the inclusion criteria (Section 3.3.1) had been steadily increasing (Table 3.1).

Table 3.1 Admission data of RPH patients in ICU satisfying study inclusion criteria (1995 - 2000)

Year	Total admissions to RPH ICU	Number of patients satisfying study inclusion criteria	Percentage of patients satisfying study inclusion criteria
1995	1614	38	2.4
1996	1600	58	3.6
1997	1601	62	3.9
1998	1378	49	3.6
1999	1413	64	4.5
2000	1514	64	4.2

RPH = Royal Perth Hospital; ICP = intracranial pressure.

As neurosurgical services expanded at RPH from 1999, the number of patients in 1999 and 2000 with ICP monitoring rose. However, based on 1999 data, it was expected that data collection for Part A and Part B of the study may take up to four years, allowing for the fact

that a larger potential recruitment pool of patients would be required to allow for those with exclusion criteria, non-consenters and any subsequent withdrawals.

3.3.4.b Part B

As for Part A, it was not possible to directly estimate effect size for Part B of this study due to the lack of published data as to the effectiveness of respiratory physiotherapy in patients with VAP. Also subject numbers for Part B were constrained by recruitment rates and VAP incidence rates from Part A. For the purpose of Part B sample size determination, a large effect size (d =1.00) (Portney & Watkins 1993 p653) and a desired power of 0.8 were set, along with an alpha (α) of 0.05. Sample size for each group for Part B of the study was thus determined to be 17 subjects (Portney & Watkins 1993 p662). This process assumed variances would be equal between the groups. If it was assumed that the incidence of VAP would be 30.0 per cent in Part A, then a minimum of 114 Part A subjects would have been necessary for Part B power to be achieved. As the Part A power calculation projected a sample population of 144 subjects, the anticipated sample size of Part B groups, even allowing for 10 per cent withdrawals, was determined to be 19 subjects per group and considered feasible.

3.4 Variables

3.4.1 Independent

The level of respiratory physiotherapy service was the independent variable. The respiratory physiotherapy interventions comprised a regimen of positioning, MH and airway suctioning, which are described in detail in Section 3.5.2. The physiotherapy services were provided by a core group of five full-time physiotherapists, under the direct supervision of the Principal Investigator, and up to seven part-time physiotherapists working independently on weekends.

In addition to routine medical and nursing care, passive limb ranges of movement were assessed daily on all subjects by a physiotherapist.

3.4.2 Dependent

The following outcome measures were considered as dependent variables:

3.4.2.a Incidence of ventilator-associated pneumonia

For this study a diagnostic algorithm, based on that of Grossman and Fein (2000), was used to diagnose and determine the incidence of VAP. Initially the suspicion of VAP was identified through the daily use of the CPIS (Table 3.2).

Table 3.2 Clinical pulmonary infection score (CPIS) *

Temperature (°C)

≥ 36.5 and ≤ 38.4 = 0 point

≥ 38.5 and ≤ 38.9 = 1 point

≥ 39 or ≤ 36 = 2 points

Blood leukocyte count (cells/mm^3)

≥ 4,000 and ≤ 11,000 = 0 point

< 4,000 or > 11,000 = 1 point + band forms ≥ 500 = + 1 point

Tracheal secretions

Scanty = 0 point

Moderate/profuse but not purulent = 1 point

Moderate/profuse and purulent = 2 point

Oxygenation: PaO_2/FiO_2

> 240 or ARDS = 0 point

≤ 240 and no evidence of ARDS = 2 points

Pulmonary radiography

No infiltrate = 0 point

Patchy/diffuse infiltrates = 1 point

Localised infiltrate = 2 points

Culture of tracheal aspirate (semi-quantitative)

Pathogenic bacteria cultured ≤ 1+ or no growth = 0 point

Pathogenic bacteria cultured > 1+ or no growth = 1 point

Same pathogenic bacteria seen on Gram stain > 1+ = 2 points

Total score = CPIS (possible range = 0 to 12)

°C = degrees Celsius, mm = millimetres; PaO_2 = arterial oxygen tension; FiO_2 = fraction of inspired oxygen; ARDS = acute respiratory distress syndrome.
* based on Pugin et al (1991).

For the purpose of this study, the suspicion of VAP was based on a threshold score of seven or greater. Flanagan et al (2000) evaluated the CPIS, with an optimum threshold score of seven, and reported a sensitivity of 85 per cent, specificity of 91 per cent, positive predictive value 61 per cent, and negative predictive value 96 per cent for VAP. In suspected cases of VAP, quantitative testing in the form of NBL was then used to confirm the diagnosis and aetiology of the VAP. This method has 73 per cent sensitivity and 96 per cent specificity for the diagnosis of pneumonia (Pugin et al. 1991). Sensitivity for NBL alone has been reported as ranging from 63 to 100 per cent, with specificity from 66 to 100 per cent (Campbell 2000; Fartoukh et al. 2003).

3.4.2.b Duration of mechanical ventilation

For the purpose of this study, the duration of MV (hours) was calculated from the time of

commencement of MV in the ICU until the subject was no longer receiving any form of invasive positive pressure ventilation, including bi-level positive airway pressure ventilation (BiPAP) or continuous positive airway pressure (CPAP) modes. Intermittent periods of time off MV as part of a weaning regimen were considered as part of the MV duration. Subjects not receiving MV for at least 12 hours continuously, and not receiving nocte MV, were considered as liberated from MV. Duration of MV whilst in transit to RPH, in the RPH emergency department, CT scanner, or operating theatre prior to admission to RPH ICU was not considered. Periods of non-invasive ventilation did not form part of the standard care of patients with ABI in the ICU at RPH and therefore were not included when determining the duration of MV.

3.4.2.c Length of intensive care unit stay

The length of ICU stay (days) was calculated from the time of admission to the ICU until the subject was either transferred from the ICU to a ward or declared deceased. Length of ICU stay is reported as 24-hour periods, or part there of, from ICU admission.

3.4.2.d Withdrawal rates

The number of subjects, from Parts A and B of the study, that did not complete their allocated intervention as per the randomisation process, was recorded. The day post-admission from which subjects did not receive their allocated intervention, along with reasons for not receiving their allocated intervention, was also noted (Section 3.3.3).

3.4.3 Other clinical variables

The following clinical information was also collected and reported:

- Arterial to inspired oxygen ratio (PaO_2/FiO_2) - best and worst over each 24-hour period of the study.
- Frequency of:
  - lobar collapse – as determined by review of daily chest x-ray by senior radiologists,
  - bronchoscopy,
  - re-ventilation and/or reintubation.
- Utilisation of antibiotic therapy for pulmonary reasons (based on positive sputum culture).
- Readmission rates to ICU.
- Mortality rates – in ICU, in hospital, and at 90 days post-admission.
- Length of hospital stay (days, in 24-hour periods, from admission to ICU until discharge to home, a rehabilitation centre or a residential care facility).

3.5 Procedures

This study was conducted at an inner city quaternary teaching hospital, RPH (850 beds),

which serves as both a first-line hospital and a referral centre. During a period of 44 months (1st November 2000 to 30th June 2004), all patients requiring admission to the ICU for more than 24 hours were screened for study eligibility. The RPH ICU is a 22 bed 'closed unit' (Oh 2003), admitting general medical, surgical, trauma, burns, cardiothoracic and neurosurgery patients, with a multidisciplinary team providing patient care under the direction of attending Intensive Care Specialists.

3.5.1 Randomisation

On admission to the ICU, the rostered physiotherapist assessed each patient for potential enrolment to this study. Once inclusion criteria had been satisfied, the physiotherapist allocated the patient into a study group as per their group allocation. Randomisation was performed by the Principal Investigator via a random numbers table (Portney & Watkins 1993 p116), with the random sequence of allocation concealed until assigned. Subjects were assigned to their groups by the enrolling physiotherapist and then received respiratory physiotherapy interventions as per their allocated group.

As soon as logistically feasible and emotionally appropriate (from the subject's family perspective) an ICU physiotherapist approached the family to provide the Study Information Sheet and Consent Form (Appendix 1). Explanation and information concerning the study were provided, and the physiotherapist endeavoured to obtain written, informed consent from the next of kin for their relative's participation in the study. Potential subjects received respiratory physiotherapy interventions as per their group allocation from admission, whilst the issue of consent was being resolved. If consent was subsequently declined, patients reverted to receiving respiratory physiotherapy interventions as per standard clinical practice based on physiotherapy assessment.

Medical and nursing staff, along with the subject and their family, were blinded to the subject's group allocation. It was not possible to have the physiotherapists administering the interventions, which included the Principal Investigator, blinded to group assignment.

Subjects in whom a VAP diagnosis was confirmed via a positive NBL specimen were transferred from Part A to Part B of the study and re-randomised. Randomisation in Part B also was performed via a random numbers table (Portney & Watkins 1993 p116). Part B subjects then received respiratory physiotherapy interventions as per the repeated randomisation process.

3.5.2 Physiotherapy intervention

In addition to standard nursing and medical care, subjects randomised to the Treatment Groups (i.e. Groups 1 and 3) received regular respiratory physiotherapy interventions that involved a regimen of positioning, MH, and airway suctioning.

3.5.2.a Positioning

At RPH, unless otherwise required from a spinal management perspective, routine

management of patients with ABI in the ICU involves maintenance of a 30° head-up position, whether in supine or side-lying. The head down tilt position is not utilised in the presence of ICP monitoring devices in the ICU at RPH. Management of certain orthopaedic injuries, such as unstable fractured spine or pelvis, may have limited or contraindicated attempts at positioning.

In terms of the positioning used for those randomised to Treatment Groups 1 and 3, each subject's position was maintained for a minimum of 15 minutes and was determined based on the physiotherapist's assessment of the subject's chest x-ray (CXR) and auscultation findings, with consideration of the stability of the subject's neurological and cardiorespiratory status to tolerate position changes.

The aim of the positioning was to change the area of lung dependency to alter ventilation-perfusion distribution, assist potential alveolar recruitment, to facilitate gravity assisted drainage of sputum, and ultimately improve oxygenation. If unilateral changes on the CXR and/or auscultation were apparent, and positioning was possible from a subject's stability and injury perspective, then the subject was positioned with the affected side uppermost, maintained with pillows. If bilateral changes were evident on assessment then positioning in left or right side-lying was alternated between each intervention. In the case where no abnormal CXR or auscultation findings were detected, positioning was determined by liaison between the nursing and physiotherapy staff, as per standard pressure area care routines. At RPH, standard pressure area care routines involve regular turns and repositioning alternating between side-lying and semirecumbent positions, approximately every three to four hours, by ICU nursing staff with the assistance of hospital orderly staff.

3.5.2.b Manual hyperinflation

In conjunction with positioning, MH was performed on all Treatment Group 1 and 3 subjects using a flow dependent Mapleson B circuit with a two litre rebreathing bag (Phoenix Medical; Preston, England) and Irwin valve (Pacific Health Care; Perth, Australia), with the same FiO_2 as delivered by the ventilator using an oxygen blender (Bird Corporation; Palm Springs, California, USA) and a gas flow rate of 12 l/min. The MH was performed by the physiotherapist only. The aim of MH was to increase alveolar ventilation, reverse atelectasis, and/or mobilise pulmonary secretions.

A manometer (Ashcroft, Dresser; Stratford, CT, USA) was incorporated into the MH circuitry so that with visual observation of the manometer the physiotherapist could ensure peak airway pressure did not exceed $40cmH_2O$ during MH. If PEEP of more than $5cmH_2O$ was required as part of the ventilatory management, a PEEP valve (Ambu International; Copenhagen, Denmark), calibrated to the same PEEP, was incorporated into the MH circuitry.

The MH technique consisted of a rate of 10-12 breaths per minute for a period of four

minutes, with approximately every third or fourth breath delivered as a MH breath, interspersed with breaths that were approximately the same volume as tidal breathing. Inhaled or exhaled tidal volumes were not able to be measured or standardised. The MH was performed utilising a one-handed technique to achieve a slow inspiration of approximately three seconds and an inspiratory pause of approximately two to three seconds to a peak airway pressure of $40cmH_2O$, followed by a rapid release of inspired gases and an uninterrupted expiration during which the bag of the MH circuit was held compressed. The aim was to achieve an inspiratory to expiratory flow ratio of less than 0.9 (Maxwell & Ellis 2003). Upon completion of MH the subject was reconnected to the ventilator on the same settings as pre-treatment.

3.5.2.c Airway suctioning

Airway suctioning, performed by the physiotherapist, immediately followed the MH. Pre-oxygenation (using the inbuilt feature of the ventilator) prior to the suction procedure was utilised as it is standard physiotherapy practice at RPH. The suction technique involved use of clean, non-sterile gloves with single use, sterile-sleeved open catheter system (Maersk Indoplas; Sydney, Australia) via a sterile connector (Bronch Safe with Stress Reliever: Mayo Healthcare; Rosebery, Australia) attached to the endotracheal or tracheal tube. The catheter was advanced until a cough was stimulated or until resistance was met. Prior to each suction pass, the site of the catheter insertion was wiped with an alcohol-cleansing swab (Briemar Nominees; Koo Wee Rup, Victoria, Australia) to minimise the potential for infection. The Bronch Safe adaptor allows suction with less interruption of MV and minimises the loss of PEEP. Intermittent suctioning during catheter withdrawal then occurred, with the entire airway suctioning procedure limited to less than 15 seconds. A new sterile-sleeved catheter was used for each suction pass. No more than two suction passes were performed following MH, in order to minimise stimulation and limit potential increases in ICP.

3.5.2.d Treatment duration

During a single respiratory physiotherapy treatment a minimum of two and a maximum of four cycles of MH and suctioning were performed in the selected position (3.5.2.a). There was no standardised rest period between cycles of MH and suctioning, although a couple of minutes generally elapsed, during which time the physiotherapist disposed of the used suction catheter, changed gloves and cleaned their hands (as per RPH ICU infection control procedures), and prepared the MH circuit and ventilator prior to the next cycle of MH. The number of cycles, along with rest periods between cycles, was determined from clinical assessment by the physiotherapist and subject stability during the treatment. This amounted to, on average, 30 minutes of respiratory physiotherapy per treatment. For subjects randomised to the Treatment Groups, the regimen of respiratory physiotherapy treatment was repeated six times per 24-hour period and continued until the subject was weaned from mechanical ventilatory support.

The respiratory physiotherapy interventions were provided from within existing clinical services. For the duration of the study the provision of physiotherapy services to the ICU at RPH was via three overlapping shifts: early shift (0700 – 1530), evening shift (1330 – 2200), and night shift (2130 – 0730).

3.5.3 Control group

Subjects randomised to the Control Groups (i.e. Group 2 or 4) received standard nursing and medical care but did not receive respiratory physiotherapy interventions. In an attempt to blind nursing and medical staff to group randomisation, a physiotherapist periodically attended the bedside to assess subjects in the Control Groups, at least daily and up to a maximum of once per shift. However no respiratory interventions were performed.

3.5.4 General management

Standard medical and nursing care was provided to all subjects as per RPH ICU management guidelines. This included invasive ventilatory support titrated to deliver targeted arterial blood oxygen and carbon dioxide levels, haemodynamic support including vasopressor and other intravenous infusions to maintain MAP and desired CPP levels, sedation and active cooling for both ICP and temperature control, early enteral nutrition, and infection surveillance and antibiotic therapy as clinically appropriate.

All patients were intubated (orally) prior to inclusion in the study. The time lapse between intubation and commencement of the study protocol was less than 24 hours in all cases. All subjects had either an orogastric or nasogastric tube in-situ during MV. Selective digestive decontamination was not administered in any case. Antibiotic treatment was not routinely initiated and systematic continuous subglottic suctioning was not performed, as these are not standard practices in the RPH ICU. Percutaneous tracheostomy was performed in ICU by qualified ICU medical staff on those subjects who had been intubated for one week or more, and who were deemed to require MV, airway protection and/or assistance with airway clearance for at least a further week, as per RPH ICU standard practice. Timing of the insertion of the tracheostomy was based on clinical judgement with consideration of workload requirements, staffing availability, and subject stability.

All subjects received routine nursing care that involved pressure area care and potential position changes every three to four hours. Subjects in the Control Groups did not receive any input from physiotherapists to assist nursing staff with direction, rationale or choice of positioning, and consequently the quality, accuracy and extent of positioning in the Control Groups was not consistent with that provided to the Treatment Groups. At RPH nursing staff also perform airway suctioning on an intermittent, as required, basis utilising the same technique described, but pre-oxygenation is not the nurses' standard practice and they do not perform MH.

Additionally all subjects received assessment of passive limb range of movement once daily

by a physiotherapist. Neurological rehabilitation activities (such as postural and balance exercises) were commenced for all subjects as appropriate and indicated, as per usual physiotherapy practice during the course of their ICU stay. Such neurological rehabilitation in ICU at RPH did not commence until ICP monitoring had ceased, weaning of MV and sedation had commenced, a tracheostomy was in-situ or the subject was extubated, and cardiovascular and respiratory function were stable.

3.5.5 Data acquisition

General descriptive data for each subject, including age, gender, body mass index (BMI), history of presenting complaint, GCS (Teasdale & Jennett 1974), and APACHE II score (Knaus et al. 1985) were obtained and recorded onto data sheets by the Principal Investigator. Information on subjects' past respiratory medical history such as a diagnosis of chronic obstructive pulmonary disease (COPD), chronic sputum production, and smoking history were also obtained at the time of enrolment into the study, either from the subject's medical record or questioning of the next of kin. Data collection of the dependent variables, including the six elements of the CPIS (Table 3.2), was performed daily by the Principal Investigator. At the time of the daily data collection for the CPIS, if available data for the day allowed allocation of maximum points for some CPIS elements, then preliminary scoring was undertaken. However in the majority of cases the CPIS score was retrospectively determined on full data from the completed patient's observation chart from the previous day.

The Principal Investigator entered information from the data sheets onto a computerised database for storage and analysis.

Subjects remained in the 'intervention' phase of the study whilst they received MV. Once MV was discontinued subjects no longer received respiratory physiotherapy as per group allocation, instead reverting to receiving individualised respiratory physiotherapy based on clinical assessment, as per standard RPH physiotherapy practice. Therefore once MV had ceased, some subjects may have received respiratory physiotherapy, whilst others may not, regardless of previous group allocation during the 'intervention' phase of the study.

Data collection of some of the clinical variables was not completed until the subject was discharged from hospital.

3.5.5.a CPIS – temperature

Each subject's temperature reading was noted from the patient's observation chart where nursing staff recorded their regular monitoring of this variable. The highest and/or lowest measures were utilised in determining the score for the CPIS (Table 3.2). Nursing staff were not required to standardise the mode or site of temperature recording as this is not the standard clinical practice at RPH, although a minimum frequency of four-hourly monitoring of temperature is standard for most patients in ICU at RPH. Measures may have been via a tympanic device, a temperature sensor on an indwelling pulmonary artery catheter, or via a

Mercury thermometer placed in the axilla or mouth. Consequently there may have been variation within and between subjects when measuring this element of the CPIS.

3.5.5.b CPIS - blood leukocyte count

Blood leukocytes are measured at least once a day on most patients in ICU at RPH. A routine blood sample is obtained for each patient, usually between 0500 and 0600 and sent to the RPH laboratory for haematological processing, including determination of the white cell count. Subsequent blood samples for individual patients are forwarded to the laboratory on an 'as needed' basis throughout the rest of the day. The RPH laboratory staff were blinded to subject inclusion into this study. The highest and/or lowest measures were utilised in determining the score for the CPIS (Table 3.2).

3.5.5.c CPIS - tracheal secretions

Tracheal secretions obtained from suction manoeuvres are noted on the patient's observation chart by ICU nursing and physiotherapy staff. A standardised descriptor of quantity and sputum characteristics, based on that described by Miller (1963), is utilised in the RPH ICU. The Principal Investigator reviewed the completed previous day's patient's observation chart to allocate a score for the CPIS for tracheal secretions (Table 3.2), based on the most commonly documented descriptor.

3.5.5.d CPIS - oxygenation: PaO_2/FiO_2

In the RPH ICU, frequent arterial blood gas (ABG) sampling is undertaken via an indwelling arterial blood pressure catheter (Custom Product Monitoring Kit, Abbott Critical Care Systems, Rep. of Ireland) and analysed using a calibrated Radiometer ABL System 625 (Radiometer Medical, Copenhagen, Denmark). As the Radiometer System used for the analysis of ABGs is located in the ICU, transportation time and delay of processing of the arterial blood sample are negligible, being within one to two minutes of collection. The Radiometer System undergoes regular calibration as per the unit's and manufacturer's guidelines. Results of the ABG analysis, including the PaO_2 are recorded onto the patient's observation chart at the time corresponding to sampling. The nursing staff record observations of patient ventilatory support variables on an hourly basis, including the FiO_2. The FiO_2 and PaO_2 were noted by the Principal Investigator from the completed previous day's patient's observation chart. The highest and lowest measures were utilised in calculating the PaO_2/FiO_2 ratio, with the lowest PaO_2/FiO_2 ratio subsequently determining the oxygenation score for the CPIS (Table 3.2) and the highest being recorded as a clinical variable (as per 3.4.3).

3.5.5.e CPIS - pulmonary radiography

Each morning between 0830 and 0900, staff of the RPH Radiology Department take portable CXRs of all patients in ICU. The processed films are returned to the ICU, sorted, coded and routinely reported by a consultant radiologist or a training radiology senior registrar under

supervision. The formal report from the consultant radiologist is then available from the middle of the day. Further CXRs are performed on an 'as needed' basis throughout the rest of the day, but are not formally reported, as a routine, until the next day. The RPH radiology staff were blinded to subject inclusion into this study. The formal radiology report formed the basis of the allocation of a score for the CPIS element on pulmonary radiography (Table 3.2).

3.5.5.f CPIS - culture of tracheal aspirate

Systematic daily surveillance respiratory tract cultures were performed for all subjects in the form of an ETA specimen obtained by a physiotherapist and sent for culture and semi-quantitative analysis, usually at the beginning of the day shift. To obtain this specimen, the physiotherapist inserted a sterile, 42cm size 12 or 14 catheter (Maersk Indoplas; Sydney, Australia) via the Bronch Safe catheter mount into the ETT and advanced the catheter until a cough was stimulated or significant resistance was encountered for those subjects whose cough reflex was markedly suppressed. Sputum was then suctioned into a sterile Lukens trap container (Indoplas; Mona Vole, Sydney, Australia), labelled and sent immediately to the RPH Microbiological Department for microscopy and semi-quantitative analysis. Staff in the Microbiological Department processing the ETA specimen were blinded to the subject's group allocation. Specimens were processed in a Class II Biohazard Cabinet with microscopy and culturing following routine standardised microbiological industry accepted procedures. The initial 'plating' of the ETA specimen was for 24 hours, although if there was no growth after 24 hours, or if the organism seen in Gram stained smear was not isolated, then the media was re-incubated for a further 24 hours. As the processing of the ETA and the finalising of the reporting of the microscopy and culture required a minimum 24 hours (and up to two or three days), inclusion of this element in the CPIS score calculation was always retrospective.

3.5.6 Non broncho-alveolar lavage

In subjects in whom the CPIS was greater than seven (indicating a suspicion of VAP), the ICU physiotherapist then performed a non broncho-alveolar lavage (NBL). In performing the NBL the physiotherapist inserted a sterile, single-sheathed, 50cm, plugging telescoping catheter (Maersk Indoplas; Sydney, Australia) via the Bronch Safe catheter mount into the ETT and advanced the catheter until significant resistance was encountered. This was followed by the instillation of a 20ml lavage volume of sterile 0.9 per cent saline solution (90mg in 10ml) (Astra Pharmaceuticals; North Ryde, Sydney, Australia) over a 10 – 15 second time period and immediate re-aspiration, prior to the removal of the catheter (A'Court et al. 1993; Flanagan et al. 2000). The resulting lavage specimen was suctioned into a sterile Luken trap container (Indoplas; Mona Vole, Sydney, Australia), labelled and sent immediately to the RPH Microbiological Department for microscopy and quantitative analysis. Staff of the Microbiological Department processing the NBL specimen were blinded

to the subject's group allocation. A positive diagnosis for infection from the NBL specimen was then used as confirmation of VAP and the indication to transfer a subject from Part A to Part B of the study.

The incidence of VAP for each group was determined as the number of subjects in each group in whom a positive NBL diagnosis for infection confirmed VAP, as a proportion of total group enrolments.

3.5.7 Summary of blinding measures

- Medical and nursing staff, along with the subject and their family, were blinded to the subject's group allocation.
- In an attempt to blind nursing and medical staff to group randomisation, a physiotherapist periodically attended the bedside to assess subjects in the Control Groups, at least daily and up to a maximum of once per shift
- It was not possible to have the physiotherapists administering the interventions, which included the Principal Investigator, blinded to group assignment. However the Principal Investigator measured all outcomes of the study without informing the physiotherapists of the results.
- The RPH haematological laboratory staff processing samples to determine white cell count which formed part of the CPIS were blinded to subject inclusion into this study.
- The RPH radiology staff providing reports of subject CXR findings which formed part of the CPIS were blinded to subject inclusion into this study.
- Staff in the Microbiological Department processing the ETA specimens which formed part of the CPIS and NBL specimens which confirmed the presence of VAP were blinded to the subject's group allocation.

3.6 Statistical Analyses

Data storage and analyses were performed using the SPSS® Graduate Pack 11.5 for Windows™ statistical package. Data were analysed both using an intention to treat philosophy and analysis by treatment principle. Descriptive statistics were obtained for demographic variables for each group. All comparisons were unpaired. Success of the randomisation process in achieving comparable groups for both Part A and B of the study was assessed using Chi Square tests (on nominal data, i.e. gender, admission diagnosis, presence of chest injuries, respiratory past medical history, smoking history, chronic sputum production) and t-tests for independent samples (i.e. continuously distributed variables).

Levene's test was performed to determine if equality of variances between the groups existed. Where the Levene's test was not significant, the reported t-test results were formulated on equal variances being assumed. Chi Square tests (for categorical variables) or

t-tests were then performed on the dependent variables.

All probability (p) values were two-tailed, with a p value of less than 0.05 taken to represent a significant difference.

Periodic interim analysis of the data was performed, similar to the philosophy of sequential clinical trials, to determine if a significant difference was present between groups. It was anticipated that these interim analyses would be performed at approximately six monthly intervals by three members of an independent data and safety-monitoring board (Whitehead 2000) comprising a statistician, a health economist and a physiotherapy lecturer in cardiopulmonary sciences, all of whom had extensive research and relevant knowledge or clinical experience of physiotherapy. The reason for this periodic interim analyses was to enable the study to be ceased if the evidence was sufficiently strong to determine a significant difference between treatments, and therefore avoid unnecessary subject enrolment. In the absence of published evidence, this safety net for the study attempted to ensure that the current clinically accepted level of care was not compromised.

3.7 Ethical Issues

Support for this study was obtained from the Heads of Department of Physiotherapy and ICU at RPH prior to the submission of the proposal to the Ethics Committees. The proposal was approved by the Curtin University Human Research Ethics Committee (HR 155/2000) and the Royal Perth Hospital Ethics Committee (EC2000/071) and complied with the National Health and Medical Research Council National Statement on Ethical Conduct in Research Involving Humans. The respiratory physiotherapy interventions were standard, clinically accepted treatments; no new physiotherapy techniques were introduced during the study period.

A 'no respiratory physiotherapy interventions' group (i.e. Control Group) was included in Parts A and B of the study. However, no subject was denied access to physiotherapy interventions which have been previously shown to be effective in the literature. Additionally, in some ICUs patients do not receive routine prophylactic respiratory physiotherapy in addition to routine nursing care. Furthermore, any subject randomised to the Control Group 4 in Part B of the study had access to a '24-hour' respiratory physiotherapy service should this have been deemed necessary by the direction of the Intensive Care Specialist. Any subject deemed to require respiratory physiotherapy interventions outside of those provided as per group allocation received physiotherapy treatment, but their data were analysed in line with intention to treat philosophy and analysis by treatment principle.

Subjects were allocated a study number that remained confidential to the investigators. Data were stored securely on a computer in the Physiotherapy Department at RPH. Access to stored data was restricted to the investigators via a password.

The study did not introduce any new interventions; it only sought to investigate clinically

accepted interventions in an attempt to determine what is 'best practice'. The provision of a '24-hour' service ensured that no subject was compromised or denied access to any necessary physiotherapy services by inclusion in this study. Because patients in the ICU are generally not able to give informed consent due to the severity of their condition and the medical management they may receive, written informed consent was obtained from the patient's next of kin.

3.8 Facilities and Resources

The computing resources required for data entry and analysis for this study were available at the Physiotherapy Department at RPH and Curtin University of Technology, School of Physiotherapy. The Principal Investigator undertook all data entry for this study. Statistical advice was provided by Dr Marie Blackmore (2000 - July 2003) and Dr Ritu Gupta (July - October 2003, May – October 2004), both of whom were employed by Curtin University of Technology, School of Physiotherapy.

Physiotherapy staff who performed the respiratory physiotherapy interventions for this study were provided from within existing clinical services of the RPH Physiotherapy Department.

The existing clinical services of the ICU were sufficient to enable collection of all the dependent variables for this study by the Principal Investigator.

The specific information required to conduct the economic evaluation was obtained via consultation with key ICU staff, including the ICU Director, the Senior Respiratory Technician and the Business Manager for the Critical Care Division of RPH. The RPH Business Analysis Unit was also consulted. The Principal Investigator obtained information concerning physiotherapy workload (in terms of occasions of service and time units) from the Allied Health Systems (AHS) database (Version 2.6.1; Health Department of WA).

The expertise of a health economist, Dr Elizabeth Geelhoed, from the Health Department of WA, was obtained for the conduct of this study.

A seeding grant of AUD$5000 was received in 2001 from the Physiotherapy Research Foundation of the Australian Physiotherapy Association and was used to provide clinical support to the Principal Investigator to facilitate data collection, data collation, data entry and specific research time for this project.

No additional instrumentation was required for this study. All equipment used for data collection of the dependent variables was used as part of normal clinical management of patients in ICU and was calibrated and maintained as per the RPH and manufacturers' standards.

Chapter 4 Results

This chapter describes the findings of this study. Section 4.1 outlines the subject recruitment and allocation process for Part A. Baseline demographic data of the subjects are also provided, together with the effects of the intervention on the dependent variables, initially following an intention to treat philosophy (Section 4.1.3), and then following analysis by treatment principles (Section 4.1.6). Section 4.2 provides results from Part B of the study, following an intention to treat philosophy (Section 4.2.2) and then by analysis by treatment principles (Section 4.2.5), whilst Section 4.3 provides comparison between those subjects with and without VAP.

4.1 Part A

4.1.1 Subject recruitment and allocation

Subject recruitment commenced on 1st November 2000, following which all patients admitted to the ICU at RPH were screened for potential inclusion in the study. Recruitment ceased on 30th June 2004. During this period of just over three and a half years, a total of 5,297 patients were admitted to the ICU at RPH, 193 of whom met the study inclusion criteria (Figure 4.1). Of the 193 eligible patients, 144 were enrolled into the study representing 74.6 per cent of the total ABI population and approximately three per cent of the entire ICU population for the period. Data collection ceased in October 2004 when the last subject enrolled in the study was discharged from the acute care hospital.

4.1.2 Periodic interim analysis

Periodic interim analysis of the data was performed annually, as described in Section 3.6. The frequency of this analysis, initially planned for six-monthly intervals and to be performed at approximately the end of June and December each year, was conducted annually due to the slower than anticipated subject recruitment rate. Interim analysis was undertaken on available data in October 2001, June 2002, and March 2003. No significant differences between groups were detected for any dependent variables at any of the periodic interim analyses.

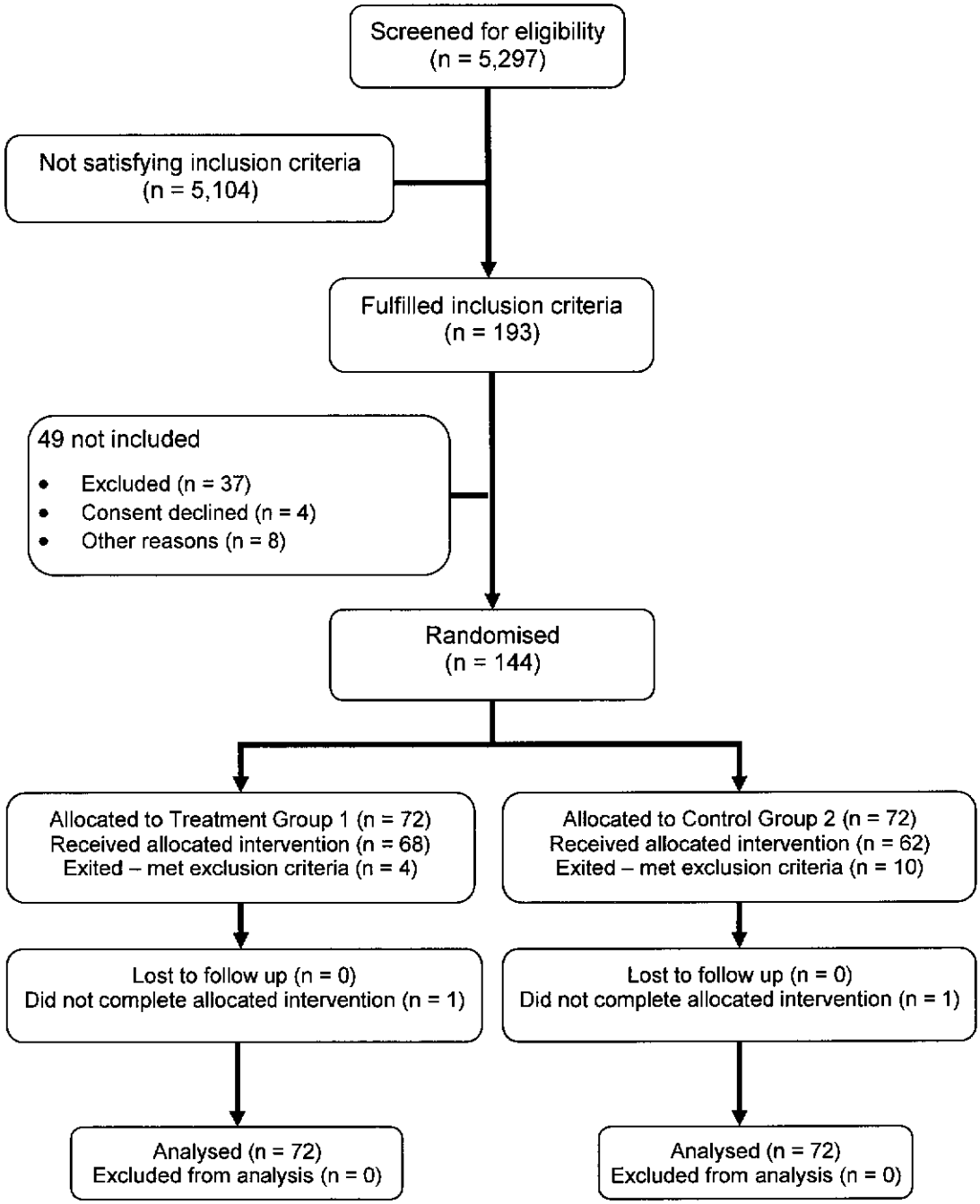

Figure 4.1 Flow diagram of the process of randomisation for Part A of the study

4.1.3 Exclusions

Reasons for the exclusion of 49 eligible subjects are listed in Table 4.1. Twenty-six of these subjects died (53.1%), 22 while in ICU (84.6%) at, on average, 81.3 hours post-admission.

Table 4.1 Reasons for exclusion of eligible subjects

Reasons	Number of subjects (n = 49)
Neurological instability (Section 3.3.2)	18
Excessive cardiorespiratory support requirements (Section 3.3.2)	9
Not for further active management	6
Consent declined	4
Physiotherapy staffing issues	4
Other issues relating to obtaining consent or randomisation	
• Next of kin non-English speaking	1
• Next of kin also a patient in ICU	1
• Next of kin in custody	1
• Alteration in initial 'not for active management' status	1
• Patient initially an 'unknown male'	1
• Respiratory physiotherapy received at another acute care facility prior to transfer to the RPH ICU	2
• Delayed insertion of ICP monitor, with physiotherapy provided prior to potential randomisation	1

n = number; ICU = intensive care unit; RPH = Royal Perth Hospital; ICP = intracranial pressure.

4.1.4 Intention to treat analysis

The following paragraph outlines the comparison of the groups undertaken to determine whether the randomisation process achieved baseline equivalence, based on an intention to treat philosophy. Groups were comparable for all variables with the exception of gender distribution and BMI. In the Treatment Group 1 there were significantly more males than females whereas the Control Group 2 had equal males and females, whilst those in the Control Group 2 had a significantly lower BMI. Results of the Levene's test suggested equality of variances between the groups existed on baseline continuous demographic variables.

4.1.4.a Demographic and descriptive data

Summary demographic data of the 144 subjects who completed the study are given in Table 4.2, with further data from the analysis of these subjects provided in Appendix 2.1.

Table 4.2 Demographic characteristics of the 144 subjects in Part A of the study

Variable		Treatment Group 1 (n = 72)	Control Group 2 (n = 72)	p value
Age (years) #		45.8 ± 19.0 17 - 85	41.1 ± 20.0 16 - 81	0.15
Gender (male/female)		51 / 21	36 / 36	0.01
Race *	Caucasian	62 (86.1)	64 (88.9)	0.36
	Aboriginal	8 (11.1)	4 (5.6)	
	Other	2 (2.8)	4 (5.6)	
BMI (kg/m^2) #		27.6 ± 5.3 18.5 – 42.1	25.5 ± 6.5 17.1 – 54.3	0.04
GCS #		5.4 ± 2.0 3 - 9	4.9 ± 2.0 3 - 9	0.21
APACHE II score #		20.3 ± 5.7 9 - 39	20.4 ± 5.6 8 - 38	0.82
History of presenting complaint *	MVA / MBA	29 (40.3)	29 (40.3)	0.53
	SAH / ICH	26 (36.1)	30 (41.7)	
	Alleged assault	7 (9.7)	2 (2.8)	
	Fall	6 (8.3)	6 (8.3)	
	Other	4 (5.6)	5 (6.9)	
Chest injuries	Yes / No	20 / 52	21 / 51	0.85
Respiratory history *	Nil	58 (80.6)	58 (80.6)	0.46
	COPD	4 (5.6)	3 (4.2)	
	Asthma	5 (6.9)	9 (12.5)	
	Other	5 (6.9)	2 (2.8)	
Smoking history*	Non	42 (58.3)	39 (54.9)	0.38
	Current	23 (31.9)	26 (36.6)	
	Ex < 6/52	0 (0.0)	2 (2.8)	
	Ex > 6/52	7 (9.7)	4 (5.6)	
Chronic sputum production	Yes / No	5 / 67	5 / 67	1.0

= for continuous data, values reported are mean ± SD, and range
* = data are numbers of subjects with percentage of group in parentheses
n = number; p = probability; SD = standard deviation; BMI = body mass index; kg = kilograms; m = metres; GCS = Glasgow coma scale; APACHE = acute physiological and chronic health evaluation; MVA = motor vehicle accident; MBA = motor bike accident; SAH = subarachnoid haemorrhage; ICH = intracranial haemorrhage; COPD = chronic obstructive pulmonary disease; Ex < 6/52 = ceased smoking within the last six weeks; Ex > 6/52 = ceased smoking over six weeks ago.

4.1.5 Intention to treat analysis: dependent variables

4.1.5.a Incidence of ventilator-associated pneumonia

In accordance with an intention to treat philosophy, analysis was performed on the 144 subjects enrolled into Part A of the study. Thirty-three subjects satisfied the criteria for the diagnosis of VAP, representing 22.9 per cent of the study population; 14 subjects (19.4%) from Treatment Group 1 and 19 (26.4%) from Control Group 2. No significant difference between groups was detected for the incidence of VAP (p = 0.32). Table 4.3 provides data for the incidence of VAP.

Table 4.3 Incidence of VAP in the 144 subjects in Part A of the study

Variable	Treatment Group 1 (n = 72)	Control Group 2 (n = 72)	p value
Incidence of VAP * (n)	14 (19.4)	19 (26.4)	0.32
VAP diagnosis day (from ICU admission) #	5.8 ± 4.0 1 - 12	5.3 ± 3.1 2 - 14	0.71
Antimicrobial therapy utilised (Yes / No)	31 / 41	33 / 39	0.74

* = data are numbers of subjects with percentages in parentheses
# = for continuous data, values reported are mean ± SD, and range
n = number; p = probability; VAP = ventilator-associated pneumonia; ICU = intensive care unit; SD = standard deviation.

Table 4.4 summarises the primary bacteria isolated in the diagnosis of VAP. The VAP was polymicrobial in 15 cases (45.4%). Four of the 17 VAP subjects with *Staphylococcus aureus* as their primary pathogen also had *Haemophilus influenzae* as a secondary pathogen. Similarly five of the 9 VAP subjects with *Haemophilus influenzae* as their primary pathogen also had *Staphylococcus aureus* isolated. Therefore, of those subjects in whom VAP was polymicrobial, in 60 per cent (nine subjects) VAP resulted from the same combination of pathogens.

Table 4.4 Primary bacteriology characteristics of subjects with VAP

Variable	Treatment Group 1 (n = 14)	Control Group 2 (n = 19)	p value
Staphylococcus aureus	7	10	0.31
Haemophilus influenzae	4	5	
Klebsiella spp.	0	1	
Acinetobacter baumanii	1	0	
Pseudomonas aeruginosa	0	1	
Enterobacter spp.	2	0	
Escherichia coli	0	2	

VAP = ventilator-associated pneumonia; n = number; p = probability.

4.1.5.b Other dependent variables

Descriptive data for the remaining dependent variables are shown in Table 4.5. Levene's test suggested equality of variances between the groups was not present for duration of MV, length of ICU stay, or length of hospital stay (Appendix Table 2.1.2). Consequently for these variables, the results and levels of significance reported are formulated on equal variances not being assumed.

Table 4.5 Duration of mechanical ventilation and length of stay for the 144 subjects in Part A of the study

Variable	Treatment Group 1 (n = 72)	Control Group 2 (n = 72)	p value
Duration of MV (hours) *	172.8 ± 119.8 138.7 16.8 – 624.2	206.3 ± 157.1 157.1 26.5 – 737.3	0.18
Length of ICU stay (hours) *	224.2 ± 122.4 208.0 21.5 – 668.0	256.4 ± 184.5 206.1 44.1 – 900.8	0.22
Length of hospital stay (days) *	36.4 ± 49.9 24.6 2.8 – 357.1	25.4 ± 20.0 21.4 1.8 – 82.0	0.09

* = data are mean ± SD, followed by median, and range
n = number, p = probability; MV = mechanical ventilation; ICU = intensive care unit; SD = standard deviation.

4.1.5.c Clinical information

Descriptive data for the clinical information monitored are shown in Tables 4.6 and 4.7. No significant differences between groups were identified for any variable. Figures 4.2 – 4.4 provide graphical views of the daily mean CPIS and PaO_2/FiO_2 data for first 14 days of MV for the subjects in Part A of the study.

Table 4.6 Clinical information for the 144 subjects in Part A of the study

Variable		Treatment Group 1 (n = 72)	Control Group 2 (n = 72)	p value
Lobar collapse *		24 (33.3)	23 (31.9)	0.86
Bronchoscopy *		2 (2.8)	6 (8.3)	0.15
Re-ventilation *		8 (11.1)	11 (15.3)	0.46
Re-admission to ICU *		2 (2.8)	2 (2.8)	1.00
Mortality *	Total #	13 (18.1)	21 (29.2)	0.12
	In ICU ^	7 (53.8)	14 (66.7)	0.46

* = data are numbers of subjects with percentages in parentheses
# = mortality within 90 days of hospital admission
^ = data are numbers of subjects with percentage of total mortality in parentheses
n = number, p = probability; ICU = intensive care unit.

Table 4.7 Daily mean CPIS and PaO_2/FiO_2 data for the subjects in Part A of the study

Variable	Group	Day of admission													
		1 (n=144)	2 (n=143)	3 (n=125)	4 (n=101)	5 (n=81)	6 (n=61)	7 (n=57)	8 (n=47)	9 (n=33)	10 (n=25)	11 (n=21)	12 (n=16)	13 (n=13)	14 (n=1)
CPIS *	1	4.0 ± 2.5	4.3 ± 2.4	5.2 ± 2.5	4.6 ± 2.4	4.3 ± 2.2	4.5 ± 2.4	4.9 ± 2.2	4.7 ± 2.1	4.6 ± 2.4	4.1 ± 1.8	4.6 ± 2.6	4.7 ± 2.9	5.2 ± 2.5	3.5 ± 2.9
	2	3.9 ± 2.3	4.7 ± 2.4	5.2 ± 2.9	4.3 ± 2.5	4.0 ± 2.4	5.1 ± 2.8	5.2 ± 2.5	5.1 ± 2.5	5.1 ± 2.0	5.7 ± 1.9	5.6 ± 1.9	4.9 ± 2.0	5.0 ± 2.6	5.4 ± 2.2
PaO_2/FiO_2 * best of day	1	401.6 ± 126.1	385.0 ± 102.0	377.1 ± 99.3	387.6 ± 91.8	385.4 ± 74.4	405.1 ± 95.9	405.5 ± 71.7	389.2 ± 70.4	389.1 ± 49.3	436.5 ± 105.6	412.6 ± 71.2	350.2 ± 36.8	394.0 ± 97.1	376.7 ± 82.5
	2	413.7 ± 134.1	401.9 ± 113.1	398.2 ± 106.9	405.1 ± 110.2	399.3 ± 99.7	395.8 ± 90.5	399.4 ± 96.5	414.5 ± 96.8	410.3 ± 114.5	402.2 ± 83.9	432.6 ± 131.9	424.9 ± 117.8	394.7 ± 170.2	491.0 ± 58.4
PaO_2/FiO_2 * worst of day	1	258.6 ± 107.0	253.7 ± 80.3	246.2 ± 80.9	261.7 ± 84.4	274.2 ± 72.1	262.0 ± 48.9	267.0 ± 65.3	277.0 ± 70.0	271.2 ± 56.4	308.0 ± 51.0	301.9 ± 78.7	244.2 ± 39.9	283.0 ± 82.0	302.8 ± 94.8
	2	268.5 ± 108.1	262.9 ± 106.2	266.0 ± 113.3	275.8 ± 112.2	300.9 ± 100.3	295.8 ± 105.2	289.9 ± 81.3	300.6 ± 95.0	263.7 ± 86.3	297.2 ± 87.4	287.1 ± 100.2	308.6 ± 103.4	256.7 ± 99.2	390.7 ± 133.3

* = data are mean ± SD; SD = standard deviation.
n = number; CPIS = clinical pulmonary infection score; PaO_2 = arterial oxygen tension; FiO_2 = fraction of inspired oxygen.

Six subjects remained in the intervention phase of the study beyond day 14 of ICU admission; summary data for day 15 and beyond for these six subjects are not presented.

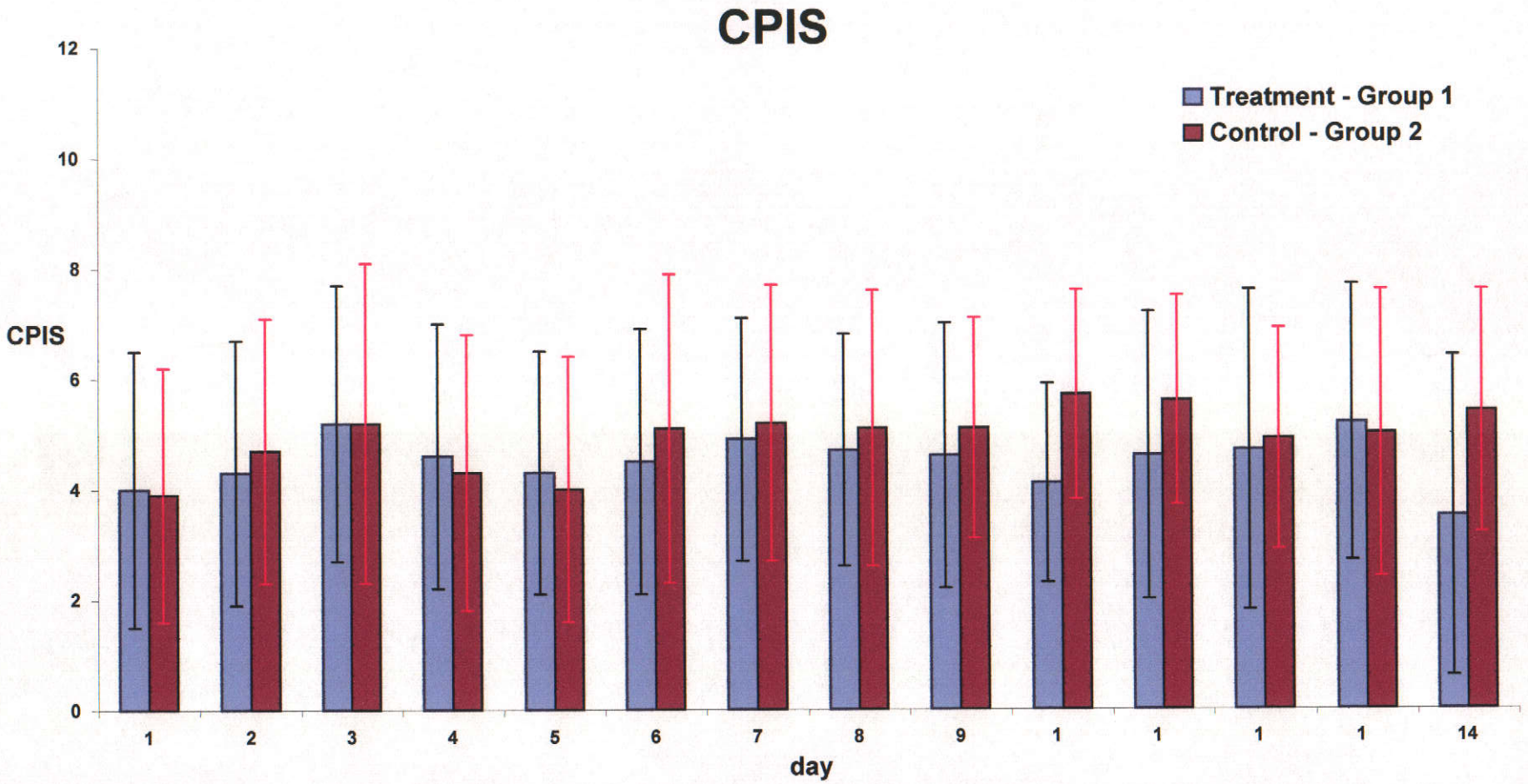

Figure 4.2 **Daily mean CPIS data for the subjects in Part A of the study**
(error bars represent standard deviation); CPIS = clinical pulmonary infection score

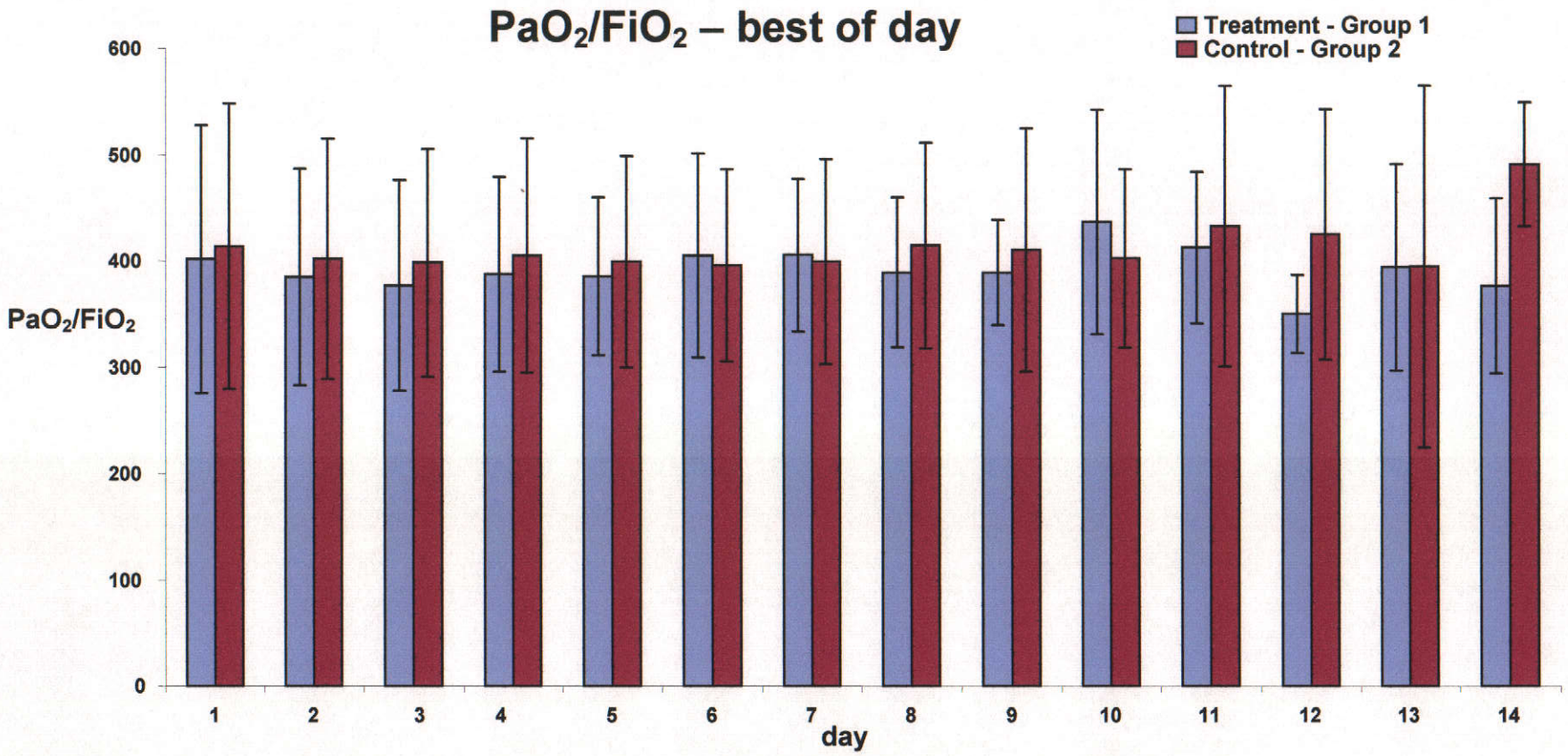

Figure 4.3 **Daily mean PaO_2/FiO_2 data (best of day) for the subjects in Part A of the study**
(error bars represent standard deviation); PaO_2/FiO_2 = arterial to inspired oxygen ratio

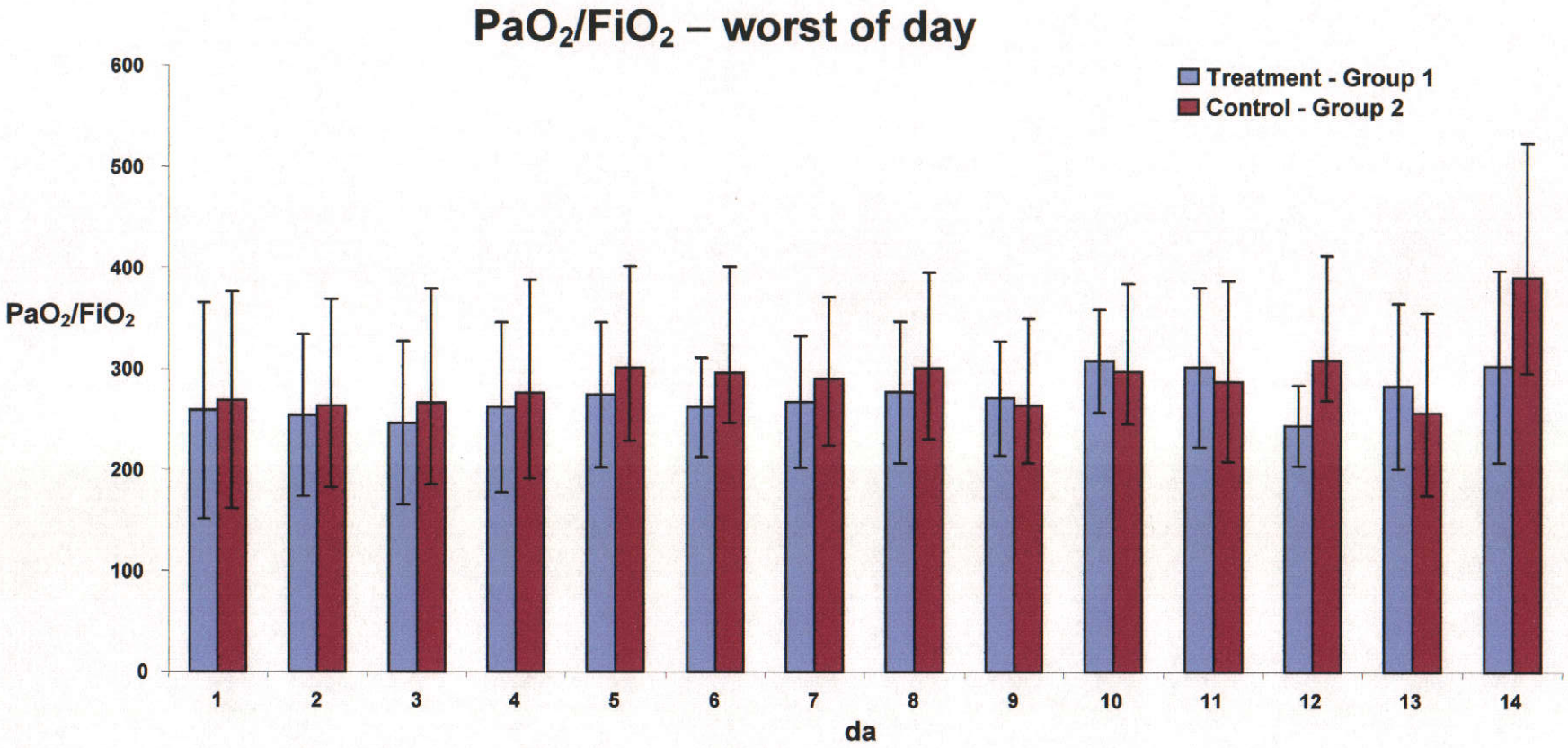

Figure 4.4 **Daily PaO_2/FiO_2 data (worst of day) for the subjects in Part A of the study**
(error bars represent standard deviation); PaO_2/FiO_2 = arterial to inspired oxygen ratio

4.1.6 Subjects not receiving all Part A allocated intervention

Sixteen subjects in Part A of the study did not receive all the study interventions as per their allocated group, representing 11.1 per cent of the study population and comprising five subjects out of 72 (6.9%) from Treatment Group 1 and 11 out of 72 (15.3%) from Control Group 2.

The ratio of subjects not receiving all their allocated study interventions in the two groups was not significantly different ($p = 0.11$). As per Section 3.6, data collection for subjects that did not receive all their allocated intervention continued and data from these 16 subjects were included and analysed in accordance with an intention to treat philosophy and analysis by treatment principles. The day post-admission from which subjects did not receive their allocated intervention was day one for one subject, day two and three – five subjects each, day four – three subjects and on day five for two subjects. Reason for subjects not receiving all study interventions, as per their allocated group, are shown in Table 4.8.

Table 4.12 Reasons why the 16 included subjects did not receive all their allocated intervention

Reasons	Treatment Group 1 (n = 5)	Control Group 2 (n = 11)
Cessation of further active management	2	6
Development of withdrawal criteria (Section 3.3.3)	1	4
Self extubation and subsequent requirement for non-invasive ventilation	1	0
Physiotherapy staffing issues	1 *	1 #

n = number
* = subject not transferred by weekend physiotherapist to Part B Control Group 4 upon VAP diagnosis
# = subject provided respiratory physiotherapy interventions by weekend physiotherapist, outside of group allocation

Eleven of these 16 subjects (68.8%) who did not receive all their interventions as per allocated group subsequently died, six in ICU and five on the neurosurgical ward, of whom four were deceased within 48 hours and one 96 hours post-discharge from ICU. This compares to 23 of the remaining 128 Part A subjects being deceased (18.0%) ($p < 0.01$). Table 4.9 provides summary comparison demographic data for the 16 subjects that did not receive all allocated interventions and the remainder of the study population, with further details in Appendix 2.2. Those who did not receive all their allocated intervention were significantly older, admitted with a lower GCS, and had a higher APACHE II score than subjects who received all their study interventions. No differences were evident in the incidence of VAP ($p = 0.67$), duration of MV ($p = 0.20$) or length of ICU stay ($p = 0.08$) between those subjects receiving all interventions and those 16 not receiving all their allocated interventions.

Table 4.9 Demographic characteristics of the 16 study subjects who did not receive all their allocated Part A intervention

Variable		Subjects not receiving all allocated Part A intervention (n = 16)	Remaining Part A subjects (n = 128)	p value
Age (years) #		54.1 ± 21.9 18 - 82	42.2 ± 18.9 16 - 85	0.02
Gender (male/female)		9 / 7	78 / 50	0.72
Race *	Caucasian	13 (81.3)	113 (88.3)	0.72
	Aboriginal	2 (12.5)	10 (7.8)	
	Other	1 (6.3)	5 (3.9)	
BMI (kg/m^2) #		28.1 ± 9.9 19 – 54	26.4 ± 5.6 17 – 48	0.41
GCS #		4.2 ± 1.9 3 - 9	5.3 ± 2.0 3 - 9	0.04
APACHE II score #		24.1 ± 6.6 15 - 39	19.9 ± 5.3 8 - 38	<0.01
History of presenting complaint *	MVA / MBA	4 (25.0)	54 (42.2)	0.12
	SAH / ICH	10 (62.5)	46 (35.9)	
	Alleged assault	0 (0.0)	9 (7.0)	
	Fall	0 (0.0)	12 (9.4)	
	Other	2 (12.5)	7 (5.5)	
Chest injuries	Yes / No	3 / 13	38 / 90	0.36
Respiratory history *	Nil	13 (81.3)	103 (80.5)	0.35
	COPD	2 (12.5)	5 (3.9)	
	Asthma	1 (6.3)	13 (10.2)	
	Other	0 (0.0)	7 (5.5)	
Smoking history *	Non	8 (50.0)	73 (57.5)	0.82
	Current	7 (43.8)	42 (33.1)	
	Ex < 6/52	0 (0.0)	2 (1.6)	
	Ex > 6/52	1 (6.3)	10 (7.9)	
Chronic sputum production	Yes / No	1 / 15	9 / 119	0.91

= for continuous data, values reported are mean ± SD, then range
* = data are numbers of subjects with percentage of Group in parentheses
n = number; p = probability; SD = standard deviation; BMI = body mass index; kg = kilograms; m = metres; GCS = Glasgow coma scale; APACHE = acute physiological and chronic health evaluation; MVA = motor vehicle accident; MBA = motor bike accident; SAH = subarachnoid haemorrhage; ICH = intracranial haemorrhage; COPD = chronic obstructive pulmonary disease; Ex < 6/52 = ceased smoking within the last six weeks; Ex > 6/52 = ceased smoking over six weeks ago.

4.1.7 Analysis by treatment

4.1.7.a Demographic and descriptive data

In accordance with analysis by treatment principles, analysis was performed on the 128 subjects in Part A of the study who completed the study interventions as per their allocated group. Summary demographic data of these 128 subjects are given in Table 4.10, whilst further details of the comparisons of these included subjects are in Appendix 2.3. Consistent with the findings of the intention to treat analysis (Section 4.1.3), groups were comparable for all demographic variables following analysis by treatment, with the exception of gender distribution and BMI.

Table 4.10 Analysis by treatment: demographic characteristics of the 128 subjects who completed interventions of Part A of the study

Variable		Treatment Group 1 (n = 67)	Control Group 2 (n = 61)	p value
Age (years) #		44.5 ± 18.5 17 - 85	39.6 ± 20.1 16 - 81	0.14
Gender (male/female)		48 / 19	30 / 31	<0.01
Race *	Caucasian	57 (85.1)	56 (91.8)	0.17
	Aboriginal	8 (11.9)	2 (3.3)	
	Other	2 (3.0)	3 (4.9)	
BMI (kg/m^2) #		27.6 ± 5.4 18.5 – 42.1	25.1 ± 5.6 17.1 – 47.6	0.01
GCS #		5.4 ± 1.9 3 - 9	5.1 ± 2.0 3 - 9	0.34
APACHE II score #		19.7 ± 5.2 9 - 34	20.0 ± 5.5 8 - 38	0.76
History of presenting complaint *	MVA / MBA	28 (41.8)	26 (42.6)	0.54
	SAH / ICH	23 (34.3)	23 (37.7)	
	Alleged assault	7 (10.4)	2 (3.3)	
	Fall	6 (9.0)	6 (9.8)	
	Other	3 (4.5)	4 (6.6)	
Chest injuries	Yes / No	19 / 48	19 / 42	0.73
Respiratory history *	Nil	54 (80.6)	49 (80.3)	0.54
	COPD	3 (4.5)	2 (3.3)	
	Asthma	5 (7.5)	8 (13.1)	
	Other	5 (7.5)	2 (3.3)	
Smoking history*	Non	40 (59.7)	33 (55.0)	0.44
	Current	21 (31.3)	21 (35.0)	
	Ex < 6/52	0 (0.0)	2 (3.3)	
	Ex > 6/52	6 (9.0)	4 (6.7)	
Chronic sputum production	Yes / No	5 / 62	4 / 57	0.84

= for continuous data, values reported are mean ± SD, and range
* = data are numbers of subjects with percentage of group in parentheses
n = number; p = probability; SD = standard deviation; BMI = body mass index; kg = kilograms; m = metres; GCS = Glasgow coma scale; APACHE = acute physiological and chronic health evaluation; MVA = motor vehicle accident; MBA = motor bike accident; SAH = subarachnoid haemorrhage; ICH = intracranial haemorrhage; COPD = chronic obstructive pulmonary disease; Ex < 6/52 = ceased smoking within the last six weeks; Ex > 6/52 = ceased smoking over six weeks ago.

4.1.8 Analysis by treatment: dependent variables

4.1.8.a Incidence of ventilator-associated pneumonia

Thirty subjects satisfied the criteria for the diagnosis of VAP, representing 23.4 per cent of the study population; 13 subjects (19.4%) from Treatment Group 1 and 17 (27.9%) from Control Group 2. No significant difference between groups was detected for the incidence of VAP (p = 0.26). Table 4.11 provides data for the incidence of VAP.

Table 4.11 Analysis by treatment: incidence of VAP in the 128 subjects who completed interventions of Part A of the study

Variable	Treatment Group 1 (n = 67)	Control Group 2 (n = 61)	p value
Incidence of VAP * (n)	13 (19.4)	17 (27.9)	0.26
VAP diagnosis day (from ICU admission) #	6.2 ± 3.9 1 - 12	5.3 ± 3.3 2 - 14	0.52
Antimicrobial therapy utilised (Yes / No)	30 / 37	28 / 33	0.90

* = data are numbers of subjects with percentages in parentheses
# = for continuous data, values reported are mean ± SD, and range
n = number; p = probability; VAP = ventilator-associated pneumonia; ICU = intensive care unit; SD = standard deviation.

4.1.8.b Other dependent variables

Descriptive data for the remaining dependent variables for the 128 subjects in Part A of the study who completed the study interventions as per their allocated group are shown in Table 4.12. Levene's test suggested equality of variances between the groups did not exist for duration of ventilation or length of ICU stay (Appendix Table 2.3.2). Consequently for duration of ventilation and length of ICU stay, the results and levels of significance reported are formulated on equal variances not being assumed.

Table 4.12 Analysis by treatment: duration of mechanical ventilation and length of stay for the 128 subjects who completed interventions of Part A of the study

Variable	Treatment Group 1 (n = 67)	Control Group 2 (n = 61)	p value
Duration of MV (hours) *	178.4 ± 121.2 154.5 24.0 – 624.2	213.6 ± 181.2 164.2 26.5 – 737.3	0.20
Length of ICU stay (hours) *	231.4 ± 120.6 208.2 35.5 – 668.0	266.8 ± 190.6 230.3 44.1 – 900.8	0.22
Length of hospital stay (days) *	37.6 ± 51.2 24.6 2.8 – 357.1	27.9 ± 20.5 24.3 1.8 – 82.0	0.17

* = data are mean ± SD, followed by median, and range
n = number, p = probability; MV = mechanical ventilation; ICU = intensive care unit; SD = standard deviation.

4.1.8.c Clinical information

Descriptive data for the clinical information collected are shown in Table 4.13. No significant differences between groups were identified in any variable, based on analysis by treatment.

Table 4.13 Analysis by treatment: clinical information for the 128 subjects who completed interventions of Part A of the study

Variable		Treatment Group 1 (n = 67)	Control Group 2 (n = 61)	p value
Lobar collapse *		22 (32.8)	19 (31.1)	0.84
Bronchoscopy *		2 (3.0)	6 (9.8)	0.11
Re-ventilation *		8 (11.9)	10 (16.4)	0.47
Re-admission to ICU *		2 (3.0)	2 (3.3)	0.92
Mortality *	Total #	10 (14.9)	13 (21.3)	0.35
	In ICU ^	5 (50.0)	10 (76.9)	0.18

* = data are numbers of subjects with percentages in parentheses
# = mortality within 90 days of hospital admission
^ = data are numbers of subjects with percentage of total mortality in parentheses
n = number, p = probability; ICU = intensive care unit.

4.1.9 Summary of Part A results

All 5,297 patients admitted to the ICU at RPH between 1st November 2000 and 30th June 2004 were screened for potential inclusion in the study, of whom 193 met the inclusion criteria. Of the 193 eligible patients, 144 were enrolled into the study representing 74.6 per cent of the total ABI population and approximately three per cent of the entire ICU population for the period.

Seventy-two subjects were randomised to Treatment Group 1 and 72 to Control Group 1. Groups were comparable for all demographic variables with the exception of gender distribution and BMI. Sixteen subjects (11.1%) in Part A of the study did not receive all the study interventions as per their allocated group, comprising five subjects from Treatment Group 1 (6.9%) and 11 from Control Group 2 (15.3%), which did not represent a significant difference between the two groups. Cessation of further active management and development of withdrawal criteria (such as the development of excessive respiratory support requirements or unstable neurological status) were the primary reasons for subjects not receiving all study interventions as per their allocated group. Those who did not receive their allocated intervention were significantly older, admitted with a lower GCS, and had a higher APACHE II score than subjects who completed receiving their study intervention.

Whether using an intention to treat philosophy or following analysis by treatment principles, the incidence of VAP, duration of MV or length of ICU stay in adults with ABI were not significantly different between the Treatment and Control Groups. Clinical variables such as the daily CPIS and PaO_2/FiO_2 ratio, lobar collapse, requirement for bronchoscopy or re-ventilation, and mortality also were not significantly different between the Treatment and Control Groups.

4.2 Part B

4.2.1 Subject recruitment and allocation

Subject recruitment for Part B commenced on 1st November 2000, following which all Part A subjects underwent daily surveillance for potential diagnosis of VAP and transfer to Part B. Recruitment for Part B ceased on 30th June 2004.

Thirty-three subjects (22.9%) from Part A of the study satisfied the criteria for the diagnosis of VAP and were transferred to Part B and re-randomised, as outlined in Figure 4.5. Data collection for Part B was completed on 2nd July 2004 when the last subject enrolled in Part B of the study was discharged from the acute care hospital.

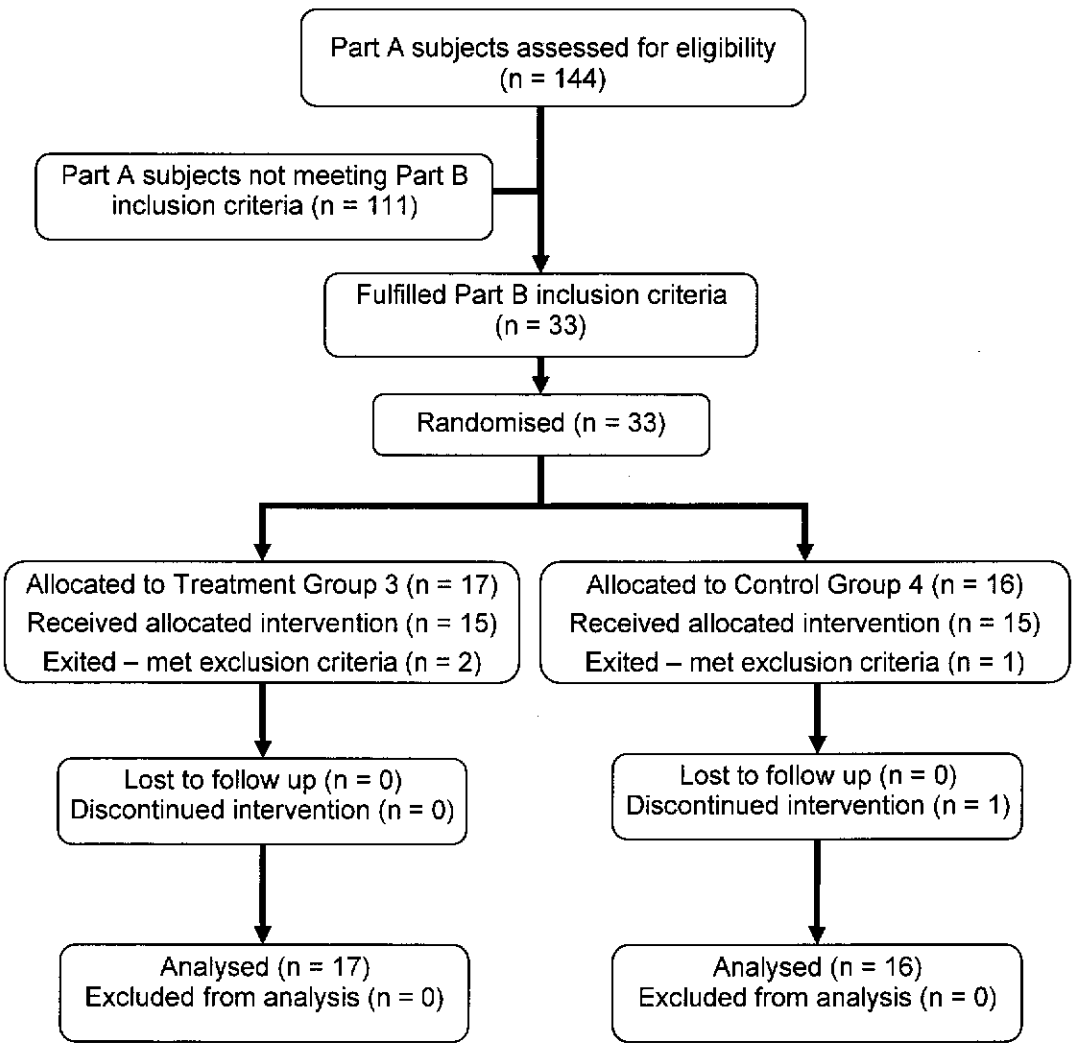

Figure 4.5 Flow diagram of the process of randomisation for Part B of the study

Table 4.14 details the results of the randomisation process into Part B, with reference to subject's preceding Part A group allocation. Only nine subjects (27.3%) crossed over between the Treatment and Control Groups from Part A to Part B. A significant difference between group randomisation in Part A and subsequent group allocation in Part B is evident, with a disproportionate number of subjects from Part A Treatment Group 1 being randomised to Part B Treatment Group 3 and similarly a disproportionate number of subjects from Part A Control Group 2 were randomised to Part B Control Group 4 ($p < 0.01$). There was no difference between groups for the day of VAP diagnosis post-admission to the ICU (Table 4.3).

Table 4.14 Part B group allocation of the 33 subjects, with reference to Part A intervention

Group allocation *		Part B		p value
		Treatment Group 3 (n = 17)	Control Group 4 (n = 16)	
Part A	Treatment Group 1 (n = 14)	11 (64.7)	3 (18.8)	<0.01
	Control Group 2 (n = 19)	6 (35.3)	13 (81.2)	

* = values are numbers of subjects with percentages in parentheses.
n = number; p = probability.

4.2.2 Part B - Intention to treat analysis

4.2.2.a Demographic and descriptive data

Demographic information of the 33 subjects who completed Part B of the study are summarised in Table 4.15 with details of comparison in Appendix 3.1. No significant differences were apparent between the groups for these demographic variables, suggesting randomisation resulted in groups for Part B that were comparable. Results of the Levene's test suggested equality of variances between the Part B groups existed on all demographic variables.

Table 4.15 Demographic characteristics of the 33 Part B subjects

Variable		Treatment Group 3 (n = 17)	Control Group 4 (n = 16)	p value
Age (years) #		34.1 ± 16.3 16 - 72	37.9 ± 17.8 16 - 66	0.52
Gender (male/female)		12 / 5	9 / 7	0.39
Race *	Caucasian	17 (100.0)	14 (87.5)	0.13
	Aboriginal	0 (0.0)	0 (0.0)	
	Other	0 (0.0)	2 (12.5)	
BMI (kg/m^2) #		26.4 ± 6.2 19.2 – 42.1	27.0 ± 7.4 19.5 – 47.6	0.81
GCS #		4.5 ± 2.0 3 - 8	4.9 ± 1.9 3 - 8	0.55
APACHE II score #		21.0 ± 6.2 11 - 34	18.2 ± 6.4 5 - 27	0.22
History of presenting complaint *	MVA / MBA	10 (58.8)	7 (43.8)	0.70
	SAH / ICH	3 (17.6)	5 (31.3)	
	Alleged assault	0 (0.0)	1 (6.3)	
	Fall	3 (17.6)	2 (12.5)	
	Other	1 (5.9)	1 (6.3)	
Chest injuries	Yes / No	7 / 10	7 / 9	0.88
Respiratory history *	Nil	11 (64.7)	10 (62.5)	0.64
	COPD	1 (5.9)	3 (18.8)	
	Asthma	4 (23.5)	2 (12.5)	
	Other	1 (5.9)	1 (6.3)	
Smoking history *	Non	9 (52.9)	9 (60.0)	0.30
	Current	7 (41.2)	4 (26.7)	
	Ex < 6/52	0 (0.0)	2 (13.3)	
	Ex > 6/52	1 (5.9)	0 (0.0)	
Chronic sputum production	Yes / No	1 / 16	2 / 14	0.51

= for continuous data, values reported are mean ± SD, and range
* = data are numbers of subjects with percentage in parentheses
n = number; p = probability; SD = standard deviation; BMI = body mass index; kg = kilograms; m = metres; GCS = Glasgow coma scale; APACHE = acute physiological and chronic health evaluation; MVA = motor vehicle accident; MBA = motor bike accident; SAH = subarachnoid haemorrhage; ICH = intracranial haemorrhage; COPD = chronic obstructive pulmonary disease; Ex < 6/52 = ceased smoking within the last six weeks; Ex > 6/52 = ceased smoking over six weeks ago.

4.2.3 Part B - Intention to treat analysis: dependent variables

4.2.3.a Duration of mechanical ventilation and length of stay

Descriptive data for the dependent variables are shown in Table 4.16. Levene's test suggested equality of variances between the groups existed (Appendix Table 3.1.2). No significant differences were detected in the dependent variables for Part B of the study.

Table 4.16 Duration of mechanical ventilation and length of stay for the 33 subjects in Part B of the study

Variable	Treatment Group 3 (n = 17)	Control Group 4 (n = 16)	p value
Duration of MV (hours) *	342.0 ± 185.3 301.0 101.0 – 737.3	351.0 ± 174.7 299.7 90.2 – 715.8	0.89
Length of ICU stay (hours) *	384.7 ± 179.6 342.0 101.0 – 747.7	397.9 ± 190.7 323.5 90.2 – 900.8	0.84
Length of hospital stay (days) *	46.5 ± 41.8 33.8 4.2 – 178.1	32.4 ± 19.9 27.6 3.8 – 82.0	0.23

* = data are mean ± SD, followed by median, and range
n = number, p = probability; MV = mechanical ventilation; ICU = intensive care unit; SD = standard deviation.

4.2.3.b Clinical information

Descriptive data for the clinical information monitored are shown in Tables 4.17 and 4.18. No significant differences between groups were identified with the exception of the incidence of lobar collapse, which was significantly higher in the Control Group 4. Figures 4.6 – 4.8 provide graphical views of the daily mean CPIS and PaO_2/FiO_2 data for the first 14 days of MV for the subjects in Part B of the study.

Table 4.17 Clinical information for the 33 subjects in Part B of the study

Variable		Treatment Group 3 (n = 17)	Control Group 4 (n = 16)	p value
Lobar collapse *		2 (11.8)	7 (43.8)	0.04
Bronchoscopy *		1 (5.9)	2 (12.5)	0.51
Re-ventilation *		2 (11.8)	1 (6.3)	0.58
Re-admission to ICU *		0 (0.0)	0 (0.0)	1.00
Mortality *	Total #	2 (11.8)	2 (12.5)	0.95
	In ICU ^	2 (100.0)	2 (100.0)	0.95

* = data are numbers of subjects with percentages in parentheses
# = mortality within 90 days of hospital admission
^ = data are numbers of subjects with percentage of total mortality in parentheses
n = number, p = probability; ICU = intensive care unit.

Table 4.18 Daily mean CPIS and PaO_2/FiO_2 data for the subjects in Part B of the study

Variable	Group	Day post-VAP diagnosis													
		1 (n=33)	2 (n=33)	3 (n=31)	4 (n=31)	5 (n=27)	6 (n=25)	7 (n=24)	8 (n=21)	9 (n=15)	10 (n=14)	11 (n=8)	12 (n=6)	13 (n=6)	14 (n=6)
CPIS *	3	9.1 ± 1.0	7.8 ± 2.6	8.0 ± 1.6	7.4 ± 2.6	6.7 ± 2.0	6.3 ± 2.0	5.8 ± 2.4	6.3 ± 2.6	5.3 ± 1.9	5.5 ± 3.9	4.2 ± 2.2	5.3 ± 1.5	4.0 ± 1.0	3.7 ± 1.2
	4	9.1 ± 1.1	7.8 ± 1.9	7.3 ± 2.4	6.8 ± 2.6	7.2 ± 2.8	6.6 ± 3.0	5.5 ± 2.6	6.4 ± 3.0	5.5 ± 3.2	4.9 ± 3.2	5.8 ± 1.3	7.3 ± 1.2	6.3 ± 1.5	6.3 ± 0.6
PaO_2/FiO_2 * best of day	3	290.8 ± 104.3	335.1 ± 73.4	367.3 ± 109.0	329.0 ± 71.3	369.7 ± 74.2	349.2 ± 87.9	357.0 ± 104.4	358.1 ± 78.1	336.5 ± 115.3	361.4 ± 106.0	426.0 ± 108.3	426.3 ± 135.4	434.0 ± 65.8	504.0 ± 49.1
	4	367.6 ± 107.6	367.3 ± 101.2	399.3 ± 107.2	384.3 ± 103.6	353.4 ± 110.5	384.3 ± 86.9	383.0 ± 90.5	391.4 ± 104.9	454.6 ± 77.5	433.0 ± 91.5	400.8 ± 97.1	466.7 ± 179.2	408.3 ± 87.8	439.3 ± 86.9
PaO_2/FiO_2 * worst of day	3	183.9 ± 61.1	193.1 ± 71.2	210.2 ± 63.8	218.7 ± 81.6	251.6 ± 61.2	254.4 ± 79.3	235.0 ± 91.8	221.0 ± 71.6	245.5 ± 116.2	246.0 ± 140.9	333.3 ± 133.5	352.7 ± 105.4	292.0 ± 50.6	411.7 ± 135.5
	4	205.1 ± 44.6	221.6 ± 60.7	249.1 ± 96.5	262.6 ± 106.5	240.7 ± 125.9	273.4 ± 97.9	265.2 ± 95.1	246.0 ± 73.8	278.0 ± 57.5	283.0 ± 60.2	328.8 ± 78.8	322.3 ± 87.2	306.3 ± 58.6	337.0 ± 51.7

* = data are mean ± SD; SD = standard deviation.
n = number; CPIS = clinical pulmonary infection score; PaO_2 = arterial oxygen tension; FiO_2 = fraction of inspired oxygen.

Four subjects remained in the intervention phase of Part B of the study beyond day 14 post-VAP diagnosis; summary data for day 15 and beyond for these four subjects are not presented.

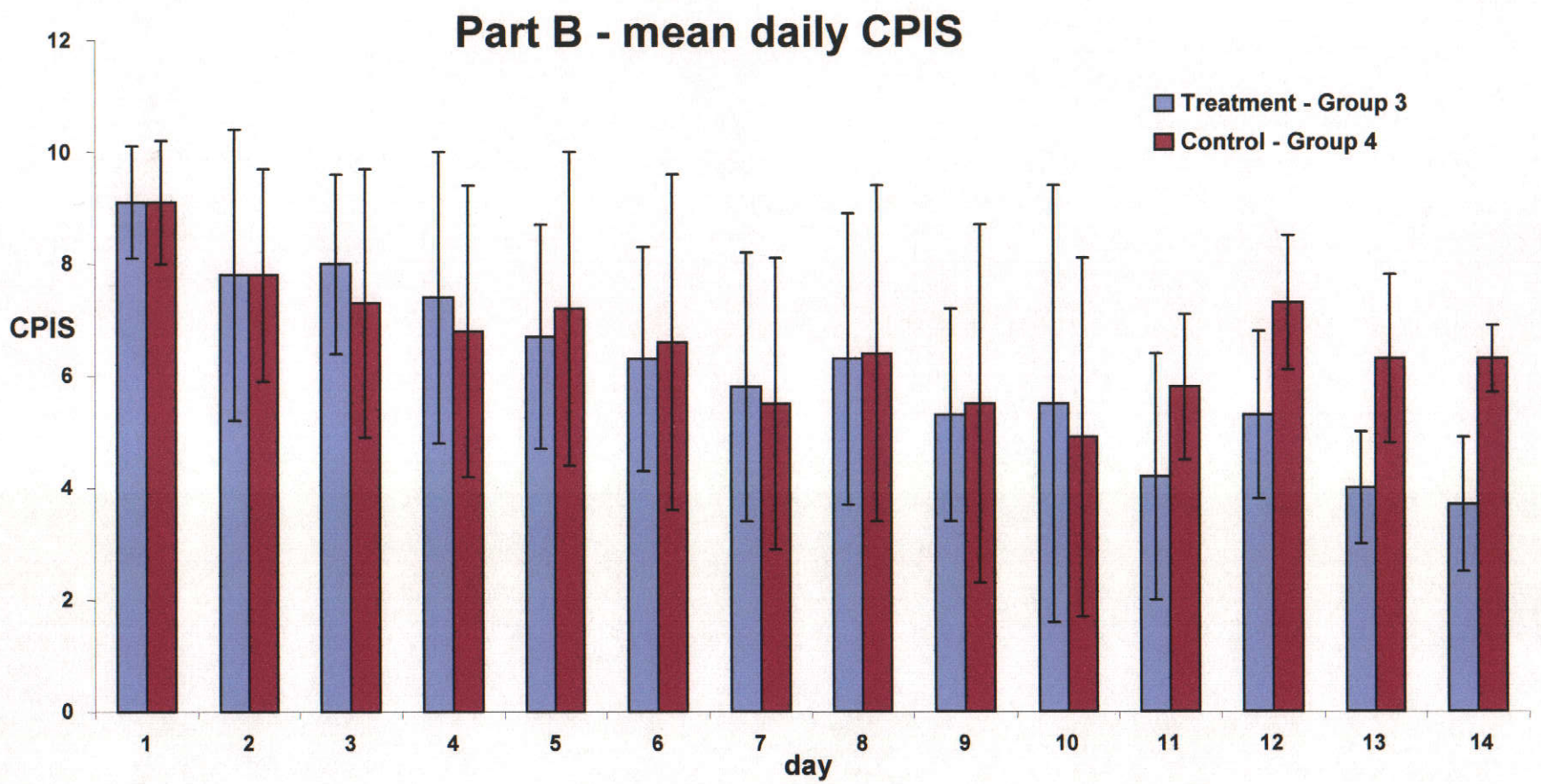

Figure 4.6 **Daily mean CPIS data for the subjects in Part B of the study**
(error bars = standard deviation); CPIS = clinical pulmonary infection score

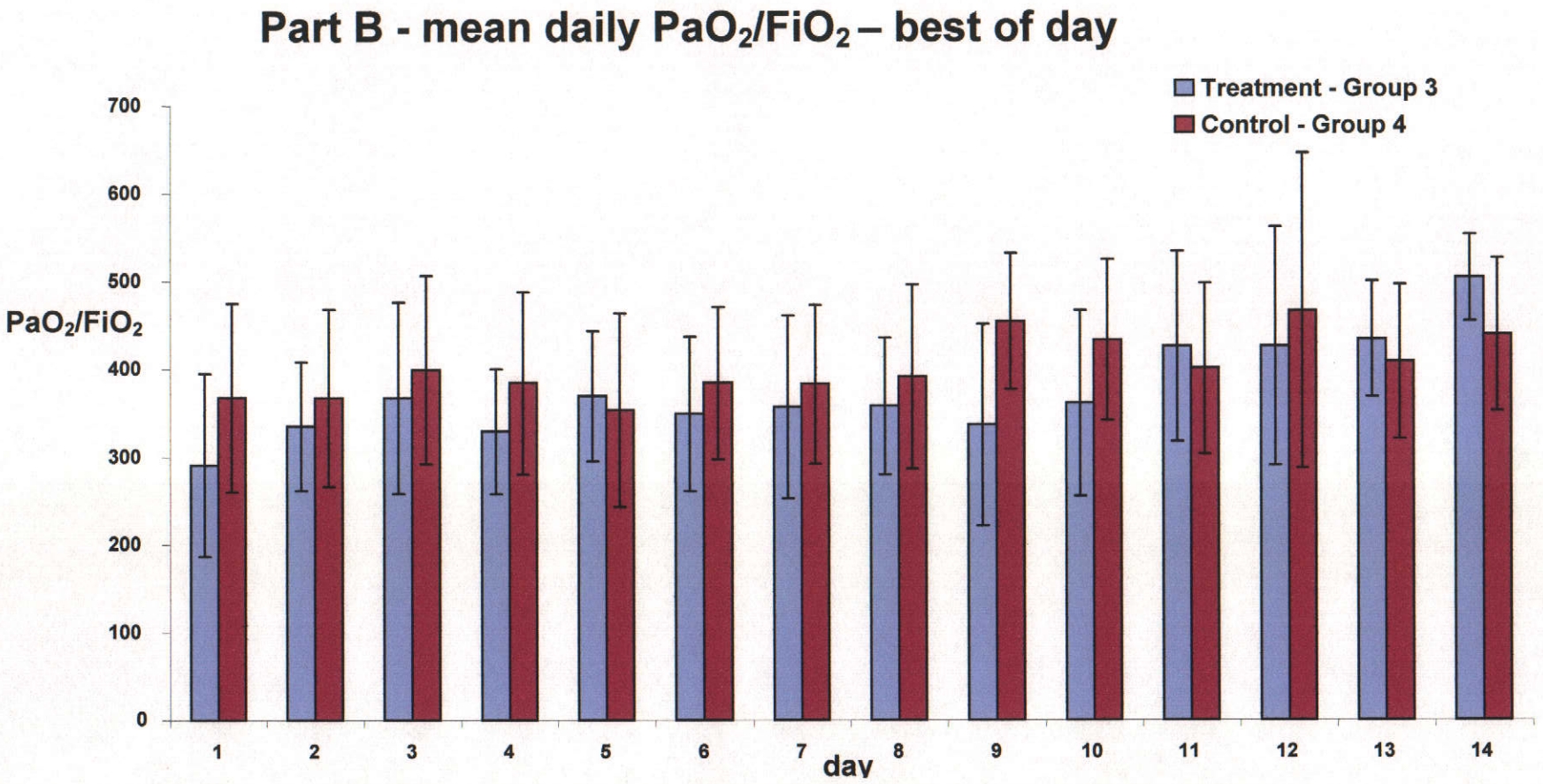

Figure 4.7 **Daily mean PaO_2/FiO_2 data (best of day) for the subjects in Part B of the study**
(error bars = standard deviation); PaO_2/FiO_2 = arterial to inspired oxygen ratio

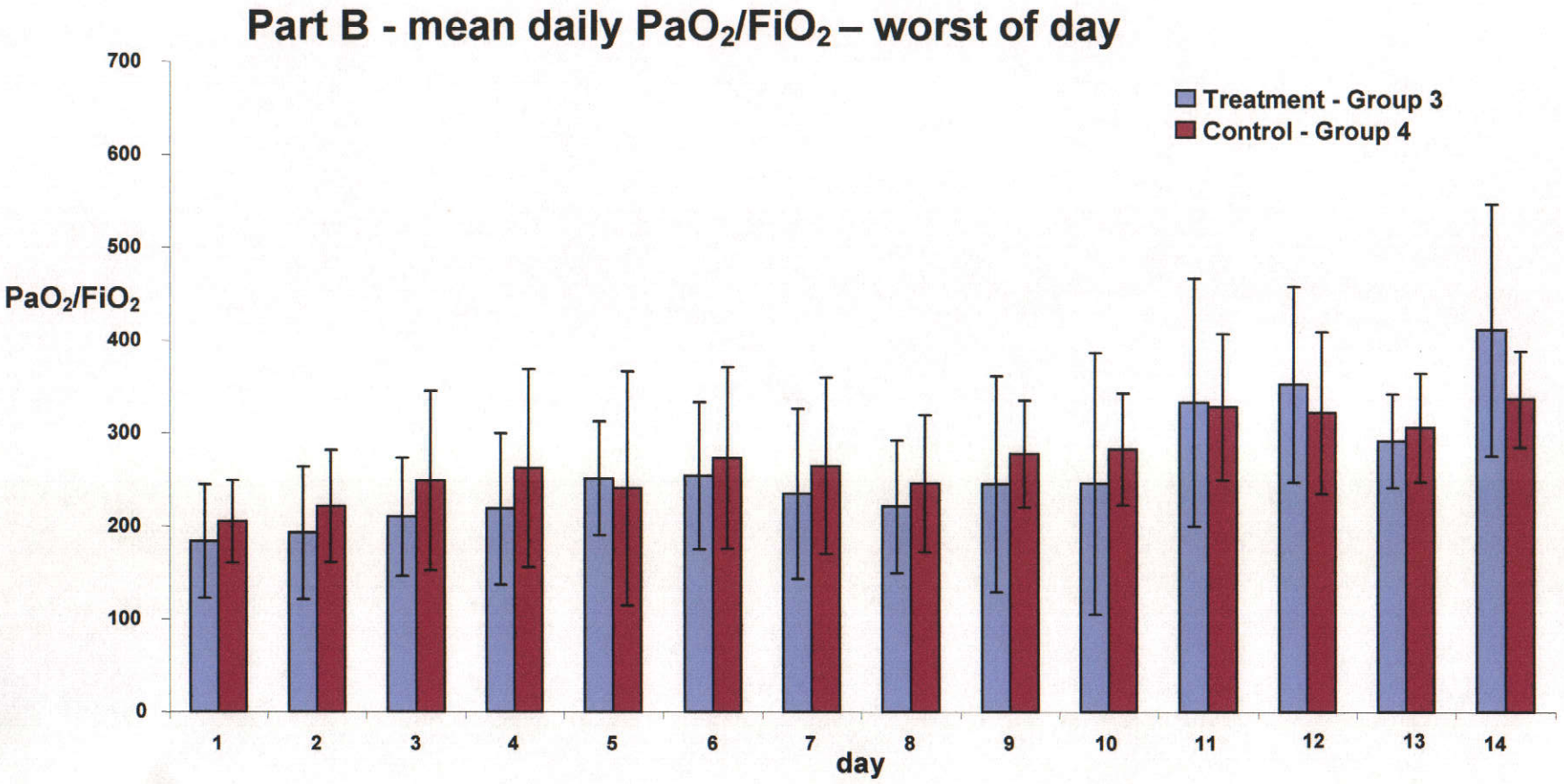

Figure 4.8 **Daily PaO_2/FiO_2 data (worst of day) for the subjects in Part B of the study**
(error bars = standard deviation); PaO_2/FiO_2 = arterial to inspired oxygen ratio

4.2.4 Subjects not receiving all Part B allocated interventions

Of the 33 Part B subjects, four did not receive all their allocated intervention, two from the Treatment Group 3 and the two from Control Group 4. The subjects did not receive all their allocated intervention from Treatment Group 3 due to the development of exclusion criteria (use of nitric oxide ventilation in one subject, and cardiovascular instability requiring temporary trans-venous pacing wire insertion in the other subject), whilst in Control Group 4 one subject was incorrectly randomised by the physiotherapist and another developed exclusion criteria in the form of a tracheoesophageal fistula. No significant difference in the ratio of subjects not receiving all their allocated study interventions between groups existed ($p = 0.95$). As per Section 3.6, data collection for subjects who did not receive all their allocated intervention was continued and data from these four subjects were included and analysed in accordance with an intention to treat philosophy and analysis by treatment principle.

These four subjects who did not receive all their allocated Part B intervention all survived to 90 days post-admission, as compared to four of the remaining 29 Part B subjects being deceased (13.8%). Table 4.19 provides comparison demographic data between the four subjects who did not receive all allocated interventions and the remainder of the study population. Those who did not receive all their allocated intervention were admitted with a higher GCS, and with these limited numbers, mechanism of ABI differed and more subjects had a positive smoking history. No significant differences were detected in the duration of MV ($p = 0.41$) or length of ICU stay ($p = 0.10$) between those subjects completing Part B interventions and those four not receiving all their allocated Part B interventions (Appendix Table 3.2.2).

Table 4.19 Demographic characteristics of the four subjects not receiving all their allocated Part B interventions

Variable		Subjects not receiving all allocated Part B interventions (n = 4)	Remaining Part B subjects (n = 29)	p value
Age (years) #		48.8 ± 19.5 26 - 72	34.2 ± 16.1 16 - 66	0.11
Gender (male/female)		1 / 3	20 / 9	0.09
Race *	Caucasian	4 (100.0)	27 (85.7)	0.59
	Aboriginal	0 (0.0)	0 (0.0)	
	Other	0 (0.0)	2 (14.3)	
BMI (kg/m^2) #		26.0 ± 8.2 19.6 – 37.5	26.8 ± 6.6 19.2 – 47.6	0.84
GCS #		6.8 ± 2.5 3 - 8	4.5 ± 1.7 3 - 8	0.02
APACHE II score #		18.8 ± 6.2 14 - 27	19.8 ± 6.5 5 - 34	0.76
History of presenting complaint *	MVA / MBA	1 (25.0)	16 (55.2)	0.04
	SAH / ICH	2 (50.0)	6 (20.7)	
	Alleged assault	1 (25.0)	0 (0.0)	
	Fall	0 (0.0)	5 (17.2)	
	Other	0 (0.0)	2 (6.9)	
Chest injuries	Yes / No	2 / 2	12 / 17	0.74
Respiratory history *	Nil	3 (75.0)	18 (62.1)	0.79
	COPD	0 (0.0)	4 (13.8)	
	Asthma	1 (25.0)	5(17.2)	
	Other	0 (0.0)	2 (6.9)	
Smoking history *	Non	1 (25.0)	17 (60.7)	0.02
	Current	1 (25.0)	10 (35.7)	
	Ex < 6/52	1 (25.0)	1 (3.6)	
	Ex > 6/52	1 (25.0)	0 (0.0)	
Chronic sputum production	Yes / No	0 / 4	3 / 26	0.50

= for continuous data, values reported are mean ± SD, then range
* = data are numbers of subjects with percentage of Group in parentheses
n = number; p = probability; SD = standard deviation; BMI = body mass index; kg = kilograms; m = metres; GCS = Glasgow coma scale; APACHE = acute physiological and chronic health evaluation; MVA = motor vehicle accident; MBA = motor bike accident; SAH = subarachnoid haemorrhage; ICH = intracranial haemorrhage; COPD = chronic obstructive pulmonary disease; Ex < 6/52 = ceased smoking within the last six weeks; Ex > 6/52 = ceased smoking over six weeks ago.

4.2.5 Part B - Analysis by treatment

4.2.5.a Demographic and descriptive data

In accordance with analysis by treatment principles, analysis was performed on the 29 subjects in Part B of the study who completed the study interventions as per their allocated group. No significant differences between groups were evident with demographic and descriptive variables. Summary demographic results of these 29 subjects are given in Table 4.20, with supplementary details of comparisons for Part B demographic and dependent variables given in Appendix 3.3.

Table 4.20 Analysis by treatment: demographic characteristics of the 29 subjects who completed interventions of Part B of the study

Variable		Treatment Group 3 (n = 15)	Control Group 4 (n = 14)	p value
Age (years) #		32.1 ± 13.8 16 - 65	36.4 ± 18.4 16 - 66	0.48
Gender (male/female)		11 / 4	9 / 5	0.60
Race *	Caucasian	15 (100.0)	12 (85.7)	0.13
	Aboriginal	0 (0.0)	0 (0.0)	
	Other	0 (0.0)	2 (14.3	
BMI (kg/m^2) #		26.0 ± 5.7 18.5 – 42.1	27.6 ± 7.7 17.1 – 47.6	0.55
GCS #		4.1 ± 1.6 3 - 8	4.9 ± 1.8 3 - 8	0.22
APACHE II score #		21.9 ± 6.0 11 - 34	17.5 ± 6.4 5 - 27	0.06
History of presenting complaint *	MVA / MBA	9 (60.0)	7 (50.0)	0.78
	SAH / ICH	2 (13.3)	4 (28.6)	
	Alleged assault	0 (0.0)	0 (0.0)	
	Fall	3 (20.0)	2 (14.3)	
	Other	1 (6.7)	1 (7.1)	
Chest injuries	Yes / No	6 / 9	6 / 8	0.88
Respiratory history *	Nil	10 (66.7)	8 (57.1)	0.71
	COPD	1 (6.7)	3 (21.4)	
	Asthma	3 (20.0)	2 (14.3)	
	Other	1 (6.7)	1 (7.1)	
Smoking history*	Non	9 (60.0)	8 (61.5)	0.52
	Current	6 (40.0)	4 (30.8)	
	Ex < 6/52	0 (0.0)	1 (7.7)	
	Ex > 6/52	0 (0.0)	0 (0.0)	
Chronic sputum production	Yes / No	1 / 14	2 / 12	0.50

= for continuous data, values reported are mean ± SD, and range
* = data are numbers of subjects with percentage of group in parentheses
n = number; p = probability; SD = standard deviation; BMI = body mass index; kg = kilograms; m = metres; GCS = Glasgow coma scale; APACHE = acute physiological and chronic health evaluation; MVA = motor vehicle accident; MBA = motor bike accident; SAH = subarachnoid haemorrhage; ICH = intracranial haemorrhage; COPD = chronic obstructive pulmonary disease; Ex < 6/52 = ceased smoking within the last six weeks; Ex > 6/52 = ceased smoking over six weeks ago.

4.2.6 Part B - Analysis by treatment: dependent variables

4.2.6.a Duration of mechanical ventilation and length of stay

Descriptive data for the dependent variables for the 29 subjects in Part B of the study who completed the study interventions as per their allocated group are shown in Table 4.21. Results of the Levene's test suggested equality of variances between the groups existed (Appendix Table 3.3.2).

Table 4.21 Analysis by treatment: duration of mechanical ventilation and length of stay for the 29 subjects who completed interventions of Part B of the study

Variable	Treatment Group 3 (n = 15)	Control Group 4 (n = 14)	p value
Duration of MV (hours) *	337.9 ± 190.7 301.0 101.0 – 737.3	335.4 ± 151.9 299.7 90.2 – 662.2	0.97
Length of ICU stay (hours) *	376.4 ± 182.8 342.0 101.0 – 747.7	367.3 ± 145.1 322.7 90.2 – 679.3	0.88
Length of hospital stay (days) *	46.0 ± 43.3 33.8 4.2 – 178.1	29.1 ± 18.9 24.4 3.8 – 82.0	0.19

* = data are mean ± SD, followed by median, and range
n = number, p = probability; MV = mechanical ventilation; ICU = intensive care unit; SD = standard deviation.

4.2.6.b Clinical information

Descriptive data for the clinical information monitored are shown in Tables 4.22 and 4.23. With the exception of a higher incidence of lobar collapse noted in the Control Group 4, no significant differences between groups were identified.

Table 4.22 Analysis by treatment: clinical information for the 29 subjects who completed interventions of Part B of the study

Variable		Treatment Group 3 (n = 15)	Control Group 4 (n = 14)	p value
Lobar collapse *		1 (6.7)	6 (42.9)	0.02
Bronchoscopy *		1 (6.7)	1 (7.1)	0.96
Re-ventilation *		2 (13.3)	1 (7.1)	0.58
Re-admission to ICU *		0 (0.0)	0 (0.0)	1.00
Mortality *	Total #	2 (13.3)	2 (14.3)	0.94
	In ICU^	2 (100.0)	2 (100.0)	0.94

* = data are numbers of subjects with percentages in parentheses
# = mortality within 90 days of hospital admission
^ = data are numbers of subjects with percentage of total mortality in parentheses
n = number, p = probability; ICU = intensive care unit.

4.2.7 Summary of Part B results

Thirty-three subjects (22.9%) from Part A of the study satisfied criteria for the diagnosis of VAP and were transferred to Part B. For Part B subjects, there was a significant difference between their group randomisation in Part A and subsequent group allocation in Part B. There was no difference between groups for the day of VAP diagnosis post-admission to the ICU.

Of the 33 Part B subjects, four did not complete their allocated intervention, two from the Treatment Group 3 and the two from Control Group 4. The subjects did not complete their allocated intervention from Treatment Group 3 due to the development of exclusion criteria, whilst in Control Group 4 one subject was incorrectly randomised by the physiotherapist and another developed exclusion criteria in the form of a tracheoesophageal fistula. No significant difference between groups in the ratio of subjects not completing their allocated Part B study interventions existed.

The Part B Groups were comparable for all demographic variables. Whether using an intention to treat philosophy or following analysis by treatment principles, regular respiratory physiotherapy in those ABI subjects with VAP did not appear to expedite recovery in terms of reducing duration of MV or length of ICU stay. With the exception of a greater incidence of lobar collapse in the Control Group, clinical variables such as the daily CPIS and PaO_2/FiO_2 ratio, requirement for bronchoscopy or re-ventilation, and mortality were not significantly different between the Part B Treatment and Control Groups.

4.3 Comparison between subjects with and without ventilator-associated pneumonia

The following section provides comparison between those subjects with and without VAP, based on intention to treat philosophy. Subjects with a VAP were significantly younger, were admitted with a lower GCS and more likely to have been admitted with a chest injury (Table 4.23). Duration of MV and length of ICU stay were significantly increased in subjects with VAP, and there was a trend for increased length of hospital stay but wide variability (Table 4.24). See also Appendix 4 for additional data of the comparison between subjects with and without VAP.

Table 4.23 Comparison of demographic characteristics between the non-VAP and VAP subjects

Variable		Non-VAP subjects (n = 111)	VAP subjects (n = 33)	p value
Age (years) #		45.7 ± 19.8 16 - 85	36.0 ± 16.9 16 - 72	0.01
Gender (male/female)		66 / 45	21 / 12	0.67
Race *	Caucasian	95 (85.6)	31 (93.9)	0.13
	Aboriginal	12 (10.8)	0 (0.0)	
	Other	4 (3.6)	2 (6.1)	
BMI (kg/m^2) #		26.5 ± 5.8 17.1 – 54.3	26.7 ± 6.7 19.2 – 47.6	0.88
GCS #		5.3 ± 2.0 3 - 9	4.6 ± 1.8 3 - 8	0.08
APACHE II score #		20.3 ± 5.7 8 - 39	20.5 ± 5.4 11 - 34	0.90
History of presenting complaint *	MVA / MBA	41 (36.9)	17 (51.5)	0.15
	SAH / ICH	48 (43.2)	8 (24.2)	
	Alleged assault	8 (7.2)	1 (3.0)	
	Fall	7 (6.3)	5 (15.2)	
	Other	7 (6.3)	2 (6.1)	
Chest injuries	Yes / No	27 / 84	14 / 19	0.04
Respiratory history *	Nil	92 (82.9)	24 (82.9)	0.27
	COPD	6 (5.4)	1 (3.0)	
	Asthma	8 (7.2)	6 (18.2)	
	Other	5 (4.5)	2 (6.1)	
Smoking history *	Non	63 (56.8)	18 (56.3)	0.04
	Current	38 (34.2)	11 (34.4)	
	Ex < 6/52	0 (0.0)	2 (6.2)	
	Ex > 6/52	10 (9.0)	1 (3.1)	
Chronic sputum production	Yes / No	7 / 104	3 / 30	0.58

= for continuous data, values reported are mean ± SD, and range
* = data are numbers of subjects with percentage in parentheses
n = number; p = probability; SD = standard deviation; BMI = body mass index; kg = kilograms; m = metres; GCS = Glasgow coma scale; APACHE = acute physiological and chronic health evaluation; MVA = motor vehicle accident; MBA = motor bike accident; SAH = subarachnoid haemorrhage; ICH = intracranial haemorrhage; COPD = chronic obstructive pulmonary disease; Ex < 6/52 = ceased smoking within the last six weeks; Ex > 6/52 = ceased smoking over six weeks ago.

Table 4.24 Comparison of duration of mechanical ventilation and length of stay for the non-VAP and VAP subjects

Variable	Non-VAP subjects (n = 111)	VAP subjects (n = 33)	p value
Duration of MV (hours) *	142.9 ± 102.5 106.8 16.8 – 431.2	346.4 ± 177.5 300.0 90.2 – 737.3	<0.01
Length of ICU stay (hours) *	195.5 ± 116.1 177.6 21.5 – 462.2	391.0 ± 182.3 324.2 90.2 – 900.8	<0.01
Length of hospital stay (days) *	28.3 ± 39.4 21.1 1.8 – 357.1	39.7 ± 33.4 30.4 3.8 – 178.1	0.14

* = data are mean ± SD, followed by median, and range
n = number, p = probability; MV = mechanical ventilation; ICU = intensive care unit; SD = standard deviation.

Comparison between those subjects with and without VAP for the descriptive data of the clinical information monitored is shown in Table 4.25. No significant differences between groups were identified, although there was a trend towards higher bronchoscopy requirements in the VAP subjects.

Table 4.25 Comparison of clinical information for the non-VAP and VAP subjects

Variable		Non-VAP subjects (n = 111)	VAP subjects (n = 33)	p value
Lobar collapse *		37 (33.3)	10 (33.3)	0.74
Bronchoscopy *		4 (3.6)	4 (12.1)	0.06
Re-ventilation *		14 (12.6)	5 (15.2)	0.70
Re-admission to ICU *		4 (3.6)	0 (0.0)	0.27
Mortality *	Total #	29 (26.1)	5(15.2)	0.19
	In ICU ^	18 (62.1)	3 (60.0)	0.93

* = data are numbers of subjects with percentages in parentheses
# = mortality within 90 days of hospital admission
^ = data are numbers of subjects with percentage of total mortality in parentheses
n = number, p = probability; ICU = intensive care unit.

4.4 Results Summary

Screening of all 5,297 patients admitted to the ICU at RPH between 1st November 2000 and 30th June 2004 identified 193 patients with ABI fulfilling inclusion criteria for potential enrolment into the study. Consent was obtained for 144 subjects (74.6%), with 72 randomised for Treatment in Part A. Twenty-seven patients were excluded due to unstable neurological, cardiac or respiratory status, six due to early limiting of active management, and consent was declined in four patients.

The Groups in Part A of the study were comparable with respect to demographic variables, the exception being BMI and gender distribution. Using intention to treat philosophy and analysis by treatment principles, there were no significant differences for the incidence of VAP, duration of MV, or length of ICU stay. Sixteen subjects in Part A of the study (11.1%) did not complete the study interventions as per their allocated group, comprising five subjects from Treatment Group 1 and 11 from Control Group 2. No significant difference existed between groups in the percentage of subjects not completing their allocated Part A study interventions ($p = 0.11$), with eight subjects having active management ceased and five developed exclusion criteria.

Thirty-three subjects (22.9%) from Part A of the study satisfied criteria for the diagnosis of VAP, and were transferred to Part B and re-randomised, 17 to Treatment Group 3 and 16 to the Control Group 4. The Groups in Part B of the study were comparable with respect to demographic variables. No significant differences were detected in the dependent variables for Part B of the study, with a similar duration of MV and length of ICU stay noted. Four subjects in Part B did not complete their allocated intervention, two from Treatment Group 3 (due to the development of exclusion criteria) and two from Control Group 4 (one subject was incorrectly randomised and another developed exclusion criteria). No significant difference between the Treatment and Control Groups for Part B existed in the percentage of subjects not completing their allocated study interventions ($p = 0.95$).

Use of a regular prophylactic respiratory physiotherapy regimen comprising of positioning, MH and suctioning, in addition to routine medical and nursing care, does not appear to significantly reduce the incidence of VAP, reduce duration of MV or length of ICU stay in adults with ABI. Furthermore, in those ABI subjects with VAP, regular respiratory physiotherapy does not expedite recovery in terms of reducing length of ventilation or ICU stay.

Compared to subjects without a VAP, those subjects with a VAP were significantly younger, were admitted with a lower GCS and more likely to have been admitted with a chest injury. Duration of MV and length of ICU stay were significantly increased in subjects with VAP, but length of hospital stay was not significantly different.

Chapter 5 Economic Evaluation

This chapter describes the findings of the economic evaluation conducted as part of this study. Section 5.1 provides the introduction, the aims and significance of the economic evaluation are detailed in Section 5.2, whilst the methodology is described in Section 5.3. Following a brief overview of the clinical study results (Section 5.4), the outcomes of the detailed cost analysis of the intervention and the cost effectiveness analysis are reported in Sections 5.5 and 5.6 respectively. Cost comparison between subjects with and without VAP is also provided in Sections 5.5 and 5.6, whilst Section 5.7 provides a conclusion to this part of the study.

5.1 Introduction

Economic evaluation assists in healthcare planning by attempting to ensure that limited resources are used in the optimal way by comparing the costs and outcomes of alternative interventions over a broad range of domains including physical health, social and psychological benefits (Turner-Stokes 2004). Economic evaluation of this application of physiotherapy to adults with ABI in the ICU is important because issues relating to limited healthcare resources are relevant to all health professionals. In an era where allocation of resources is increasingly linked to evidence based practice, it is necessary for physiotherapists to demonstrate effective delivery of care. Additionally the allocation of resources is also dependent on the availability of good quality research highlighting the effectiveness of treatment programmes (Kennedy & Stokes 2003), both on clinical and economic grounds.

As described in detail in Chapter 3, this two-part, prospective RCT investigated the effect of regular prophylactic respiratory physiotherapy on the incidence of VAP, duration of MV, and length of ICU stay in adults with ABI, as compared to a Control Group (Part A). Part B of the study randomised subjects from Part A who fulfilled the criteria for VAP into a Treatment or Control Group to establish if a regimen of regular respiratory physiotherapy influenced the outcome of VAP. Data from Parts A and B were subjected to an economic analysis, in which the costs of providing respiratory physiotherapy in relation to clinical outcomes were examined, results of which form the basis of this chapter. Provision of costing information, and comparison of costs with outcomes, may subsequently aid, and be incorporated into, discussions and may guide evaluations of the provision of respiratory physiotherapy services in ICU to adults with ABI.

Economics is particularly relevant to this study as VAP is a major cause of morbidity and mortality for patients in an ICU, although definitions and reporting mechanisms lack of standardisation and consensus. Ventilator-associated pneumonia is known to prolong length of stay, increase hospital mortality rates and may substantially increase the cost of hospitalisation two to three-fold by lengthening the duration of MV, time in ICU, and overall

hospital stay.

A precise evaluation of the morbidity and financial costs associated with VAP is complex due to the difficulty of establishing a firm diagnosis of VAP. Additionally there is also a lack of standardisation and consensus with definitions and inclusions for cost determination. To date, few interventions, including respiratory physiotherapy, have been shown to be beneficial in the prevention of VAP. The prolonged periods of hospitalisation associated with VAP give rise to its considerable financial burden; however there are very little data or evaluation in the form of cost analysis of VAP.

Data on the costs of providing respiratory physiotherapy intervention to patients with ABI in the ICU have not been published. Although respiratory physiotherapy for patients with ABI may be theoretically beneficial in reversing or preventing VAP, there are no data concerning the clinical or cost effectiveness of respiratory physiotherapy in patients with ABI. By increasing knowledge of the costs of providing respiratory physiotherapy costs for adults with ABI, and comparing costs with outcomes, it is anticipated an understanding of the costs of service provision will be facilitated, and meaningful interpretation of the clinical results obtained within the wider context of healthcare utilisation will be aided.

5.2 Aims and Significance

Evidence to date does not support or refute the role of respiratory physiotherapy to prevent and/or treat VAP in patients with ABI in the ICU. Firstly this study aimed to provide the first evaluation of the costs of respiratory physiotherapy services for patients admitted to the ICU with ABI. Secondly the study sought to provide comparison of the costs of subject outcomes based on the provision of respiratory physiotherapy.

For Part A, the cost of respiratory physiotherapy time to the point at which subjects were weaned from MV was determined for those subjects randomised to receive physiotherapy. The cost of the ICU bed day period for the duration of MV was also calculated. The aim of the economic analysis of Part A data was to examine the costs of providing respiratory physiotherapy in relation to outcomes.

In Part B, cost analysis of respiratory physiotherapy time was also undertaken, with the aim of developing cost effectiveness ratios. The aim of the economic evaluation for Part B of the study was to establish if the provision of regular respiratory physiotherapy was cost effective, based on the following outcomes: MV bed days reduced, hospital ICU bed day reduced, and life year gained.

As the role of respiratory physiotherapy for patients with ABI, with or without VAP, is presently not evidence-based or costed, results of the clinical study and economic analyses may have significant implications for physiotherapy service planning and budgeting within the ICU. Comparing the costs with outcomes, in relation to respiratory physiotherapy, provides a benchmark to allow other facilities to compare the costs of their clinical practice.

5.3 Methodology

5.3.1.a Background

Physiotherapy staff who performed the respiratory physiotherapy interventions for this study were provided from within existing clinical services of the RPH Physiotherapy Department, which is a 24-hour a day, 7-days a week rostered physiotherapy service. Medical and nursing staff, along with the subject and their family, were blinded to the subject's group allocation. Study design and methodology are detailed in Chapter 3.

Within the Health Department of WA, allied health staff, including all physiotherapists working at RPH, are required to compile daily workload data for both clinical and non-clinical time. Physiotherapy treatments, in terms of occasions of service and time units, are attributed by the physiotherapist to specific patients and recorded into the electronic database Allied Health Systems (AHS) (Version 2.6.1; Health Department of WA). An occasion of service is defined as an episode of care directly attributable to an individual patient, and may include patient assessment alone or involve an intervention. Time units refer to the duration of time (recorded in five minute blocks) accompanying a specific occasion of service to a patient, and may involve assessment alone or extend to encompass interventions such as treatment, re-evaluation and documentation. This AHS software allows patient-based reports to be generated which detail all allied health interventions attributed to a patient relating to a particular admission or episode of care. For the purpose of this study, the Principal Investigator generated a patient-based report from AHS (based on their ABI admission) for each subject enrolled in the study, from which physiotherapy workload data were manually extracted. Each physiotherapy intervention, from when the subject was admitted into the study until cessation of MV, was recorded from the patient-based report. Daily physiotherapy workload data for each subject were collated and entered into a SPSS database by the Principal Investigator under headings of occasions of service and time units for each of the three work shifts - early shift (0700 – 1530), evening shift (1330 – 2200), and night shift (2130 – 0730).

5.3.1.b The question addressed

A detailed cost analysis was firstly undertaken to describe the financial costs of physiotherapy time in providing a regimen of regular prophylactic respiratory physiotherapy to stable adult patients with ABI to prevent VAP (Part A). It was then planned to compare costs with outcomes to decide whether it is a cost-effective use of resources to provide this physiotherapy regimen to all stable adult patients with ABI to prevent VAP (Part A).

Secondly, a detailed cost analysis was undertaken to describe the financial costs of physiotherapy time in providing a regimen of regular respiratory physiotherapy to all stable adult patients with ABI who developed VAP (Part B). Cost effectiveness ratios were then to be determined to establish the cost effectiveness of providing this physiotherapy regimen to reduce days of MV, ICU bed days, and improve life years gained (Part B).

For the purpose of this study, effectiveness was defined as the number of VAP cases averted, days of MV or ICU bed days reduced, and life years gained.

5.3.1.c Procedure

The view point adopted in this analysis was that of a government service provider. The costs examined were limited to those borne directly by the RPH Critical Care Division or the RPH Physiotherapy Department. The cost analysis was limited to include only direct medical costs, and did not explore direct non-medical costs (capital works, infrastructure) and indirect costs from wider issues such as family costs (emotional, travel, loss of wages, etc), society / community costs (social security, health benefits / insurance, productivity, etc), or return to work issues (of the subjects).

For subjects randomised to the Treatment Groups in Part A and B, the regimen of respiratory physiotherapy treatment lasted 30 minutes on average, was repeated six times per 24-hour period, and continued until the subject was weaned from MV. In both Parts A and B, the Control Group received standard nursing and medical care but no respiratory physiotherapy interventions.

Physiotherapy workload data were recorded and costed for each subject. The time component was based on the time registered on AHS by the individual physiotherapist providing care to each subject.

For both Part A and Part B of the study, the cost analysis comprised assessment of costs relative to outcomes for each treatment group. Specifically the net cost of the intervention was the additional costs of respiratory physiotherapy time for each subject from admission to ICU to the point when the subject was weaned from MV. Therefore no respiratory physiotherapy costs were calculated for subjects in Control Group 2 (Part A) and Control Group 4 (Part B), as subjects randomised to these groups did not receive intervention; i.e. control subjects represent no cost, and the additional cost required for the respiratory physiotherapy intervention of subjects in the treatment groups represents the net intervention cost.

In addition to costs of physiotherapy staff time, financial costs were obtained from the RPH Business Analysis Unit and the RPH Critical Care Division Business Manager for an ICU bed day and a tertiary hospital bed day (non-ICU bed). For each subject the ICU MV bed day cost was calculated by multiplying the ICU bed day cost by their duration of MV. In Part A this cost represented the entire duration of MV for those subjects that did not have VAP, or until transfer to Part B of the study for those with VAP. For all subjects in Part B the ICU MV bed day cost represented their entire duration of MV, including their time in Parts A and B of the study. Net ICU MV bed day costs were then compared between Part A groups and related back to the net cost of the respiratory physiotherapy intervention to determine potential savings. Similar cost comparisons with outcomes between Part B groups were

undertaken.

Summary costs are expressed in Australian dollar value, using the values of the reference year 2002, and corrected where necessary using health index deflators (Australian Institute of Health and Welfare (AIHW) 2004). Appendix 5.1 provides further information on the health price index and procedures followed for their use.

5.3.1.d Costing of physiotherapy services

Costing of physiotherapy time was undertaken retrospectively and based on the Health Services Union – Department of Health – Health Service Salaried Officers State Industrial Agreement 2004 registered with the Western Australian Industrial Relations Commission, hereby referred to as the 'Award'.

Weekday early shift physiotherapy services were provided by a core team of five rotating full-time physiotherapists, plus the Principal Investigator. As the duration of postgraduate experience, and therefore level of remuneration as per the Award, was variable among the rotating full-time physiotherapists, and as the Principal Investigator was employed as a Senior Physiotherapist (Level 7.3 of the Award), it was decided to allocate a mid-point Level 3/5.5 as the average reference ordinary rate of pay level used for weekday costing.

Weekday night shift physiotherapy services at RPH are paid at a senior physiotherapist level (Level 6.1 of the Award) due to the sole physiotherapist responsibilities associated with this shift.

Weekend evening and night shift physiotherapy services at RPH are provided by experienced part-time physiotherapists. Remuneration associated with these shifts is at Level 6.3 of the Award due to the sole physiotherapist responsibilities and years of experience of the physiotherapists covering these shifts.

Costs of physiotherapy time were based on the ordinary rate of pay of the Award of:

- Level 3/5.5 for weekday early shift services,
- Level 3/5.5, plus loading of 12.5 per cent for weekday evening shift services,
- Level 6.1, plus a loading of 20.0 per cent for weekday night shift,
- Level 3/5.5, plus a loading of 50.0 per cent for Saturday early shift services,
- Level 6.3, plus a loading of 50.0 per cent for Saturday evening and night shift services,
- Level 3/5.5, plus a loading of 75.0 per cent for Sunday early shift services,
- Level 6.3, plus a loading of 75.0 per cent for Sunday evening and night shift services.

Total financial costs did not factor in shifts covered by physiotherapy staff working overtime due to sick leave or annual leave cover requirements, public holiday loading, leave loading provisions, or accrual of leave and superannuation entitlements.

The RPH ICU Physiotherapy Service provided entry level physiotherapy clinical placements throughout the duration of this study, and as part of these placements many subjects

received assessment and treatment from student physiotherapists and their supervisor. Workload data entered into AHS from student treatments are included and costed within the weekday early services, despite no remuneration being provided for this service. In the absence of student physiotherapists being involved in the treatments, the subjects in the Treatment Groups would still have required assessment and intervention by a physiotherapist. Hence it was considered appropriate to cost the student physiotherapists' input as representative of an opportunity cost that needed to be included and costed as part of the standard methodology.

Individual subject costing was calculated using the appropriate hourly rate from the Award multiplied by the treatment duration for each treatment, as entered into the AHS package.

5.3.2 Data analysis

Data storage and analyses were performed using the SPSS® Graduate Pack 11.5 for Windows™ statistical package. Clinical outcome data of the 144 subjects analysed are presented in Chapter 4.

5.4 Study Outcomes

Consent was obtained for 144 subjects, with 72 randomised for Treatment in Part A. Using intention to treat philosophy, there were no significant differences for the incidence of VAP (Treatment Group 14/72 vs. Control 19/72; $p = 0.32$), duration of MV (hr) (172.8 vs. 206.3; $p = 0.18$), or length of ICU stay (hr) (224.2 vs. 256.4; $p = 0.22$), although the trend in clinical improvement favours the Treatment Group.

Thirty-three subjects (22.9%) from Part A of the study developed a VAP, and were transferred to Part B and re-randomised, 17 to the Treatment Group 3. No significant differences were detected in the dependent variables for Part B of the study, with similar duration of MV (hr) (342.0 vs. 351.0; $p = 0.89$), and length of ICU stay (hr) (384.7 vs. 397.9; $p = 0.84$) noted.

5.5 Economic Analysis Results

This section summarises findings of the detailed cost analysis, with further details provided in Appendix 5.

5.5.1 Costs

The annual salary for Level 3/5.5 of the Award, effective from 18 January 2004, was AUD$52,911. This equated to approximately AUD$2,035 per fortnight or AUD$26.78 per hour, which served as the reference ordinary-rate-of-pay level used for physiotherapy time costing (Table 5.1).

Costs were also obtained for:

- An ICU bed day of AUD$4,125 per day, and
- A tertiary hospital bed day (non-ICU bed) of AUD$535 per day.

Table 5.1 Physiotherapy staff time costs per hour

	Shift	Costs per hour (AUD$)
Weekdays	Early	26.78
	Evening	30.13
	Night	33.82
Saturday	Early	40.17
	Evening	46.06
	Night	46.06
Sunday	Early	46.86
	Evening	53.74
	Night	53.74

AUD$ = Australian dollars; early shift (0700 – 1530), evening shift (1330 – 2200), and night shift (2130 – 0730).

5.5.2 Summary costs

Figure 5.1 illustrates the study design and the points of the study utilised in the determination of costs for respiratory physiotherapy and duration of MV.

5.5.2.a Part A

Physiotherapy workload and the cost of the intervention to the 72 Part A subjects from Treatment Group 1 were determined (Cost 1 – Figure 5.1). Summary cost analysis data are provided in Table 5.2, with occasions of service, time units and costs data presented in Appendix 5.1. For Part A, data are from the entire duration of MV for those subjects that did not have VAP, or until transfer to Part B of the study for those with VAP. The ICU MV bed day costs were calculated for each subject individually by summing their duration of MV (in days) by the daily ICU bed day rate. Total physiotherapy and ICU MV bed day costs are the summation of individual respiratory physiotherapy and ICU MV bed day costs of the 72 subjects (Figures 5.2 and 5.3).

5.5.2.b Part B

Summary physiotherapy workload and the cost of the intervention to the 17 Part B subjects from Treatment Group 3 were determined (Cost 2 & 3 – Figure 5.1). Summary Part B cost analysis data are provided in Table 5.2 and Figures 5.4 and 5.5, with occasions of service, time units and costs data presented in Appendix 5.2. Data refer only to the time that subjects were in Part B (i.e. excluding data from the time period in Part A prior to transfer to Part B). Costs for the individual and total respiratory physiotherapy for Part B were determined in the same way as Part A, but using relevant Part B time periods.

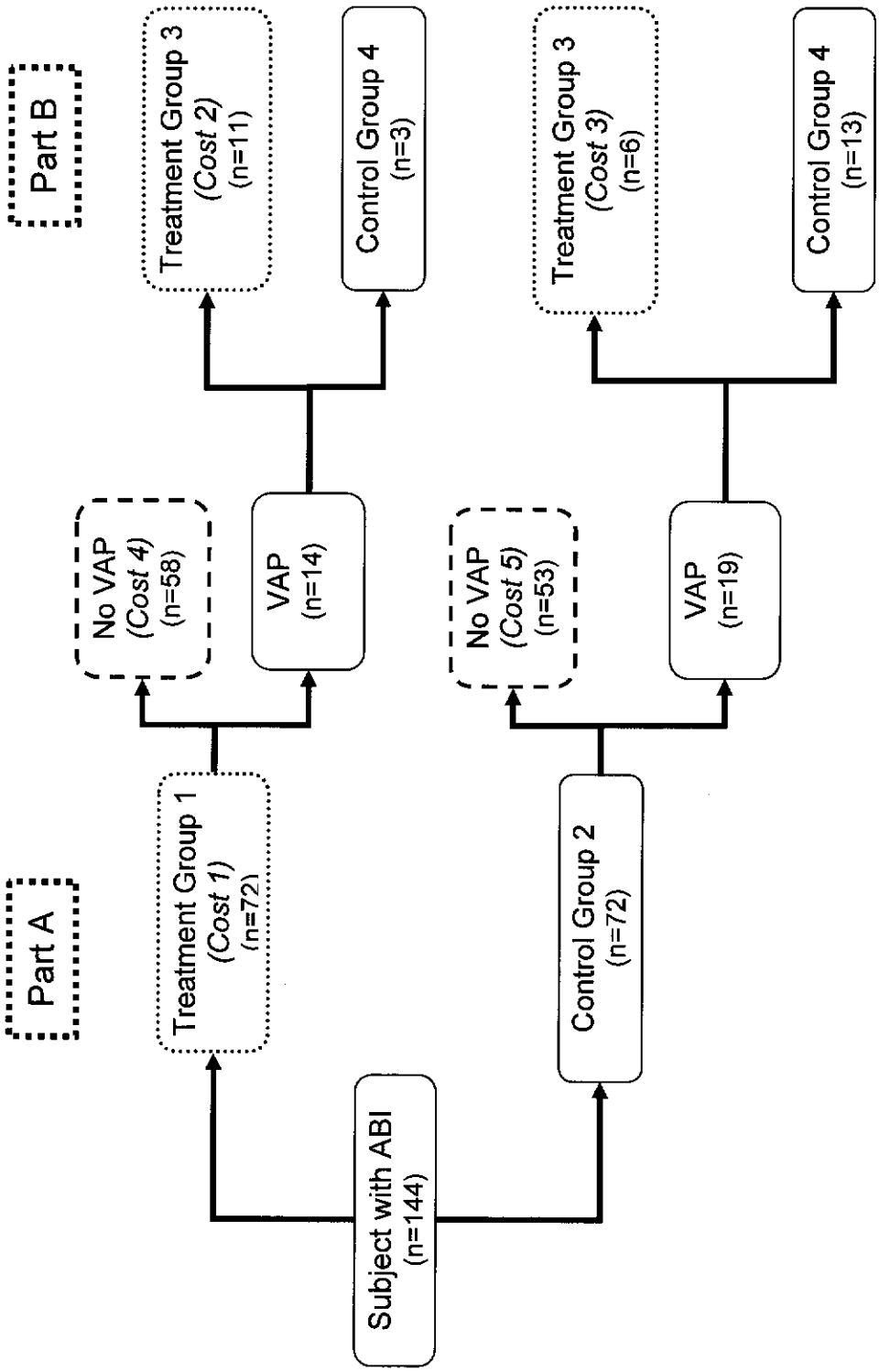

Figure 5.1 Flow diagram of study design and points of cost determination

5.5.2.c Comparison between subjects with and without ventilator-associated pneumonia

The following section provides comparison of costs between subjects with and without VAP. For non-VAP and VAP subjects, data are from the entire duration of MV. Costs for those with VAP are the summation of costs determined at Cost 1, 2, and 3 whilst costs for those without VAP are the summation of Cost 4 and 5 (Figure 5.1). Summary workload data comparing subjects with and without VAP, based on intention to treat philosophy, revealed that groups were not comparable with the number of treatment days and physiotherapy occasions of service received throughout their time in the study (Appendix 5.3).

Subjects with VAP received significantly more physiotherapy interventions over a significantly longer period of time ($p < 0.01$). Significant differences between costs for the non-VAP and VAP groups were evident (Table 5.2), with an almost a three-fold increase in ICU MV bed day costs and double the physiotherapy costs per subject for those with VAP. However the average cost of a single physiotherapy intervention was similar regardless of whether or not the subject had VAP (Table 5.2).

Table 5.2 Summary cost analysis data

		Part A (n = 72)	Part B (n = 17)	non-VAP (n = 111)	VAP (n = 33)
Per subject costs	**Physiotherapy total (AUD$)**	487 ± 399 26 – 2,074	788 ± 682 157 – 3,133	510 ± 422 68 – 2,074 (n=58)	1,029 ± 633 205 – 3,133 (n=20)
	Physiotherapy per day (AUD$)	67 ± 24 20 – 121	75 ± 18 29 – 108	66 ± 24 20 – 121 (n=58)	76 ± 18 29 – 108 (n=20)
	Physiotherapy single treatment (AUD$)	18 ± 4 11 – 34	17 ± 2 13 – 20	17 ± 4 9 – 34 (n=58)	16 ± 3 8 – 20 (n=20)
	Total ICU MV bed day (AUD$)	30,372 ± 20,612 ^ 2,893 – 103,677	41,719 ± 26,709 * 8,592 – 115,594	25,142 ± 17,821 # 2,893 – 77,745	61,092 ± 31,123 + 15,512 – 133,440
All subject costs	**Total physiotherapy (AUD$)**	35,069	13,398	29,556 (n=58)	20,570 (n=20)
	Total ICU MV bed day (AUD$)	2,186,771	709,220	2,790,716	2,016,032

data are mean ± SD, then range
min = minutes; AUD$ = Australian dollars, rounded to the nearest dollar; SD = standard deviation;
ICU = intensive care unit; MV = mechanical ventilation; % = per cent
^ mean total ICU bed day cost during MV for all 72 Part A Treatment Group 1 subjects
* mean total ICU bed day cost during MV for all 17 Part B Treatment Group 3 subjects
# mean total ICU bed day cost during MV for all 111 subjects without a VAP
+ mean total ICU bed day cost during MV for all 33 subjects with a VAP

For Figures 5.2 to 5.5 the curve superimposed on the histogram bars represents normal distribution. These graphs show clearly the skewed nature of the data and affirm the expectation that these types of data commonly show a non-normal distribution. As all subjects had ICU MV bed day costs and there would always be a cost associated with those randomised to receive physiotherapy, it was expected that distribution of costs may not follow the normal curve.

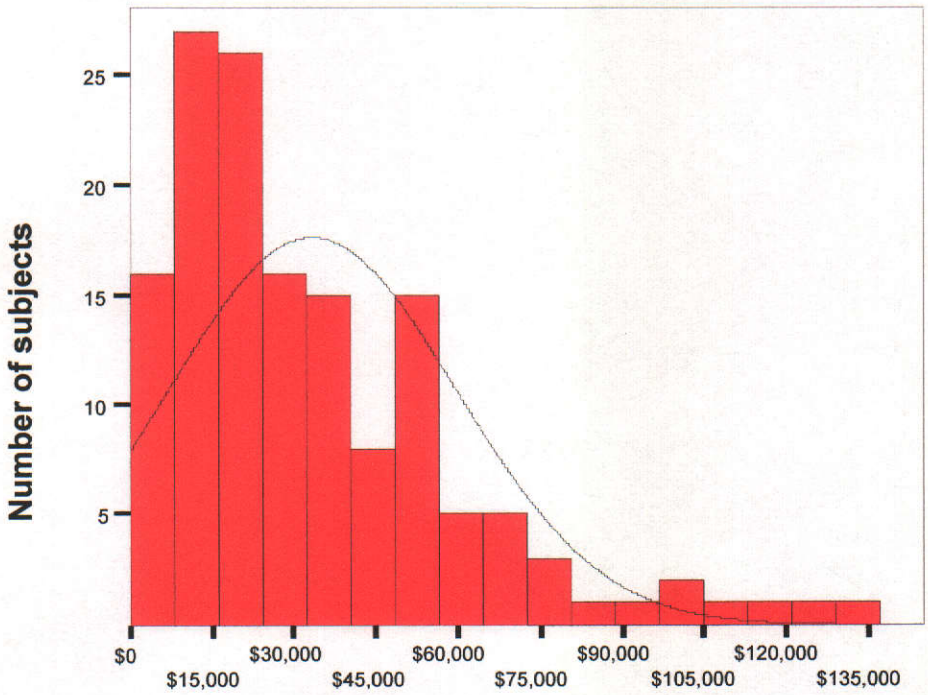

Figure 5.2 ICU MV bed day cost for all the Part A subjects

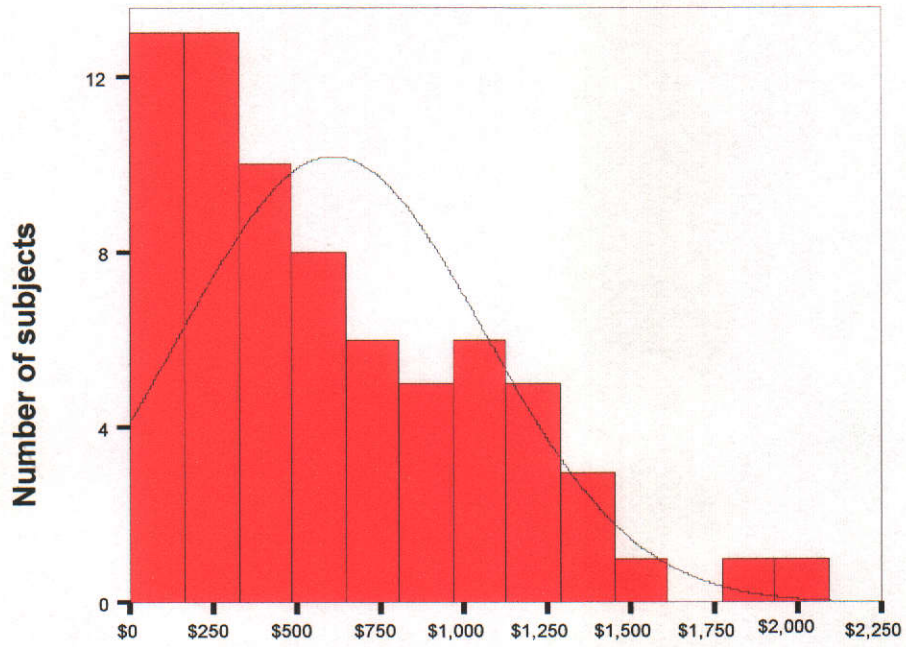

Figure 5.3 Total physiotherapy cost per subject for Part A Treatment Group 1 subjects

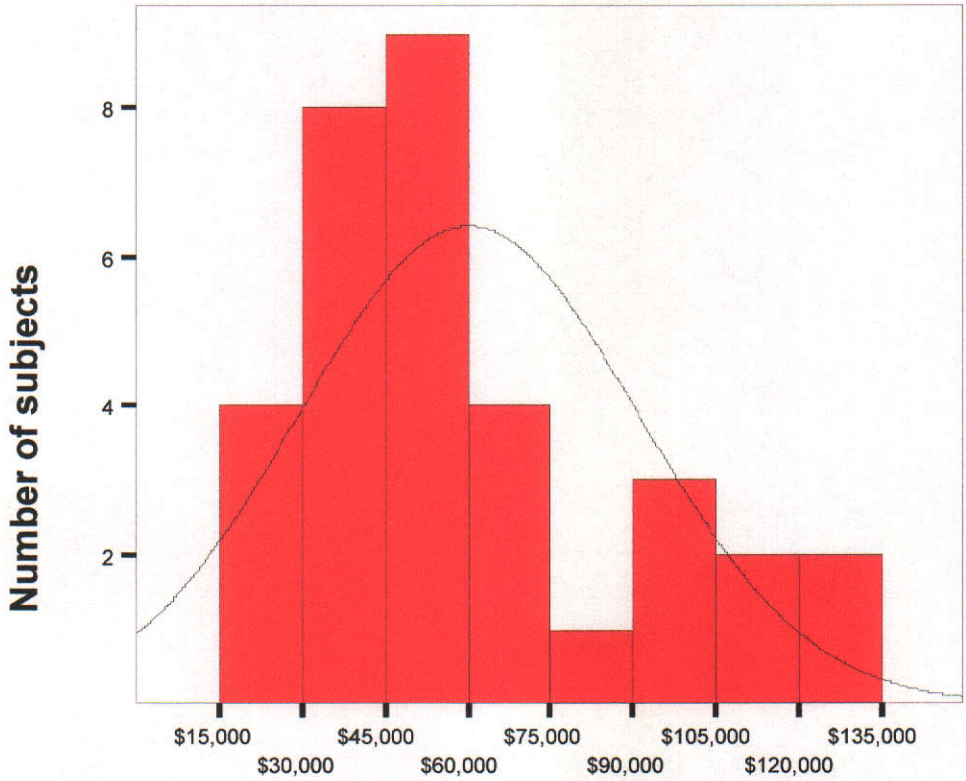

Figure 5.4 ICU MV bed day cost for all the Part B subjects

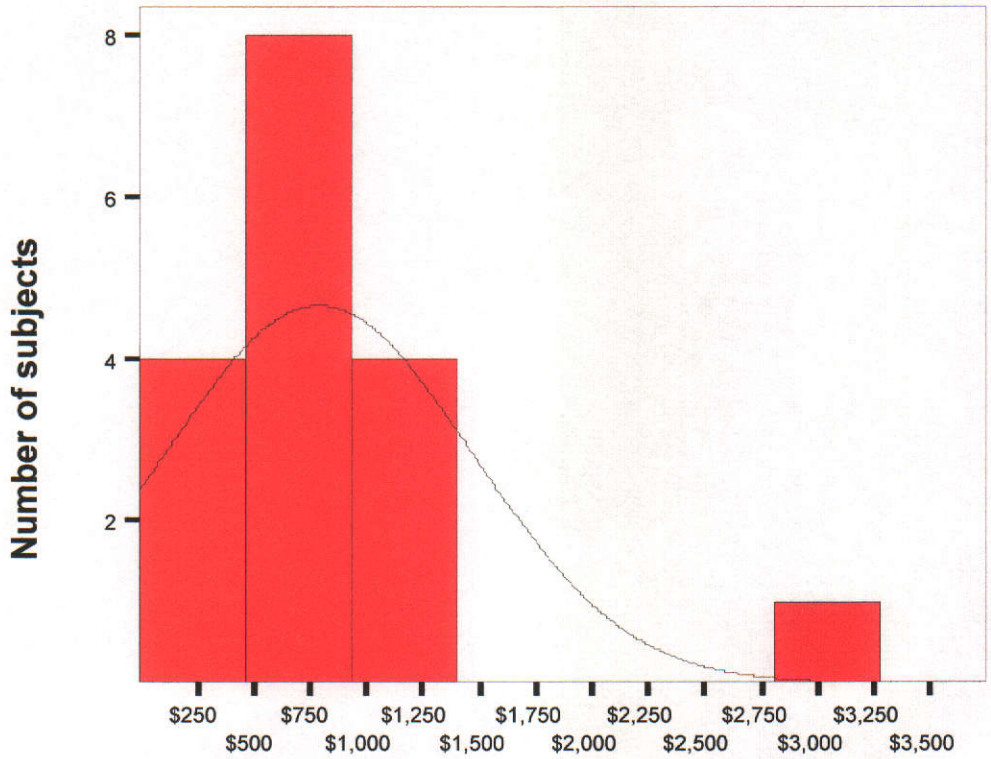

Figure 5.5 Total physiotherapy cost per subject for Part B Treatment Group 3 subjects

5.5.3 Physiotherapy cost relative to bed day cost

For patients with ABI receiving a prophylactic regimen of respiratory physiotherapy in ICU, in an attempt to prevent VAP (Part A), the average cost of physiotherapy time was $487 per individual. Comparatively the average ICU MV bed day cost for all the Part A subjects was $33,380 per individual. The cost of Part A respiratory physiotherapy time for Treatment Group 1 represents 1.7 per cent of the cost of their ICU MV bed days.

In those patients with ABI in whom VAP developed (Part B), a regimen of respiratory physiotherapy six times per day (for the remaining duration of MV following diagnosis of VAP) cost $788 per individual. Comparatively the average ICU MV bed day cost for the Part B subjects was $43,865. The cost of Part B respiratory physiotherapy time for Treatment Group 3 represents 1.8 per cent of the cost of their ICU MV bed days.

5.6 Cost Comparison with Outcomes

Statistical significance was not achieved with any differences between groups and clinical outcome measures in this study, and therefore any effectiveness of the respiratory physiotherapy intervention is not assured. However one can compare costs of the respiratory physiotherapy intervention and estimate potential savings based on differences obtained in the costs associated with the outcome measures. This section reports the findings of the cost comparison with outcomes. Section 5.6.1 summarises the reference cost determined and used to establish the financial costs of providing the respiratory physiotherapy intervention for all subjects. The summary cost data for Part A, Part B and for the comparison between subjects with and without VAP are provided in Section 5.5.2. A summary of the cost analysis is given in Section 5.5.3.

As a consequence of no significant statistical differences being detected in the clinical outcomes of incidence of VAP, duration of MV or length of ICU stay between the Treatment and Control Groups in Part A or Part B of this study, the cost effectiveness analyses undertaken should be interpreted with caution.

5.6.1.a Incidence of ventilator-associated pneumonia

Thirty-three subjects developed VAP, with no significant difference between groups detected for the incidence of VAP [14 subjects (19.4%) from Treatment Group 1 vs. 19 subjects (26.4%) from Control Group 2]. The cost analysis found that the mean ICU MV bed day cost for each subject with VAP from Treatment Group 1 was $50,756 versus $68,708 for Control Group 2 subjects (Appendix Table 5.3.8). This difference between groups in average ICU MV bed day costs of $17,952 per subject is more than three times the $5,512 total respiratory physiotherapy costs for all the 14 Treatment Group 1 subjects with VAP (Appendix Table 5.1.5). So, despite no statistically significant differences in the incidence of VAP being found, from the comparison of costs with outcomes it appears there is a 35 per cent higher ICU MV bed day cost per subject in those with VAP who did not receive a

regimen of prophylactic respiratory physiotherapy as compared to subjects with VAP who received physiotherapy.

When considering all Part A subjects, the ICU MV bed day cost for each subject without VAP was $25,142 versus $61,092 for subjects with VAP (Appendix Table 5.3.7), giving an incremental health cost of $35,950 per episode of VAP. The total cost of the respiratory physiotherapy regimen for all the 72 Treatment Group 1 subjects was calculated as $35,069 (Appendix Table 5.1.3).

Based on these finding it may be considered that a regimen of respiratory physiotherapy to all subjects, costing $487 per subject, is money well spent in pursuit of a potential cost saving of $35,950 per VAP case prevented. Alternatively, even in subjects with VAP it would appear that there is a reduction in ICU MV bed day cost in subjects receiving respiratory physiotherapy that far outweighs the cost of providing the physiotherapy and underscores the validity of investment in respiratory physiotherapy time. Based on these average figures, 74 subjects with ABI would need to receive prophylactic respiratory physiotherapy before the costs of the physiotherapy interventions exceeded the savings from one VAP case prevented.

5.6.1.b Duration of mechanical ventilation

Whilst no statistically significant difference in duration of MV was found with the provision of respiratory physiotherapy in Part A, there was a positive finding of a reduction of 33.5 hours favouring the Treatment Group. This reduction in duration of MV is equivalent to $5,758 of ICU bed day costs and represents 17.2 per cent of the total average ICU MV bed day cost for the period of MV. When considering all 144 Part A subjects, the ICU MV bed day cost for each Treatment Group 1 subject was $30,372 versus $36,389 for subjects in Control Group 2 (Appendix Table 5.1.4). A reduction of $433,207 in total ICU MV bed day cost favoured the Treatment Group 1. The total cost of the respiratory physiotherapy regimen for all the 72 Treatment Group 1 subjects was calculated as $35,069 (Appendix Table 5.1.3).

In comparison, spending on average $487 for a regimen of respiratory physiotherapy may be considered a worthwhile investment to pursue the potential savings associated with a reduced duration of MV. Twelve subjects with ABI would need to be treated before the costs of the prophylactic respiratory physiotherapy outweighed the average savings from the reduced duration of MV in one subject.

In Part B of the study, regular respiratory physiotherapy in subjects with VAP did not appear to expedite recovery, with only a difference of nine hours in duration of MV recorded, favouring the Treatment Group 3. The total ICU MV bed day cost for all 17 Treatment Group 3 subjects was $709,220, as compared to $738,321 for the 16 subjects in Control Group 4 (Appendix Table 5.2.4). In subjects who developed VAP, a regimen of respiratory physiotherapy for the remaining duration of MV following diagnosis of VAP was $788 per

subject, or alternatively $13,398 for the all 17 Treatment Group 3 subjects (Appendix Table 5.2.3). This nine hour reduction in duration of MV is equivalent to $1,547 worth of ICU bed day costs and represents only 3.5 per cent of the total average ICU bed day cost for the period of MV in those with VAP. Comparatively the $788 cost of respiratory physiotherapy in subjects with VAP would not appear to be justified in attempts to reduce the duration of MV, as the costs of physiotherapy would exceed the average cost reduction in MV after only two subjects had been treated.

5.6.1.c Length of intensive care unit stay

A reduction in length of ICU stay of 32.2 hours favouring the Treatment Group 1 was found, which did not represent a statistically significant difference between the Part A groups. The difference in length of ICU stay is of similar magnitude as the difference in duration of MV between the Part A groups. In terms of ICU bed day costs, this reduction in length of ICU stay between groups equates to $5,534 per subject, which is comparable to the difference in costs associated with reduced duration of MV.

A 13 hour reduction in length of ICU stay in favour of the Treatment Group 3 subjects was recorded, but as for Part A, this difference between Part B groups did not reach statistical significance. Similarly the difference in Part B length of ICU stay mirrors the difference between groups in duration of MV. The associated reduction in ICU bed day costs was $2,234 per subject for the Treatment Group 3 subjects.

Findings from Part A and B suggest that any potential cost effectiveness arising from respiratory physiotherapy may result from reductions in duration of MV. As there is no additional benefit from respiratory physiotherapy in reducing length of ICU stay, there does not appear to be any further cost effectiveness available other than via a reduction in duration of MV.

5.7 Conclusion

By conducting an economic evaluation in the form of a detailed cost analysis of the intervention, this study has provided the first description of the financial costs of respiratory physiotherapy time in providing interventions to patients with ABI in ICU.

For patients with ABI receiving a prophylactic regimen of respiratory physiotherapy in ICU (six times per day for their entire duration of MV), in an attempt to prevent VAP, the cost of physiotherapy time was $487 per subject. Comparatively the ICU MV bed day cost for Part A subjects was $33,389 per subject. The cost of Part A respiratory physiotherapy time for Treatment Group 1 represents 1.7 per cent of the cost of their ICU MV bed days. No statistically significant differences were detected in the clinical outcomes (i.e. incidence of VAP, duration of MV or length of ICU stay), and so it was not possible to determine with confidence any cost effectiveness ratios resulting from this regimen of prophylactic respiratory physiotherapy in patients with ABI.

In those patients with ABI who developed VAP, a regimen of respiratory physiotherapy six times per day for the remaining duration of MV following diagnosis of VAP was costed at $789 per subject. Comparatively the ICU bed day cost for subjects with VAP was $61,092 per subject. The cost of respiratory physiotherapy time for subjects with VAP represents 1.8 per cent of the cost of their ICU MV bed days. No statistically significant differences were detected in the clinical outcomes duration of MV or length of ICU stay, and so it was not possible to determine any cost effectiveness ratios resulting from this regimen of regular respiratory physiotherapy in patients with ABI and VAP.

Differences in the financial costs of respiratory physiotherapy time and ICU MV bed day costs were evident between those patients with VAP as compared to those without VAP. For patients with VAP, the respiratory physiotherapy time cost was $1,029 per subject, compared to $510 for non-VAP patients. The ICU MV bed day cost for patients with VAP was $61,092 per subject, and $25,142 for those without a VAP, giving an incremental health cost of $35,950 per episode of VAP. No differences were evident in the cost of respiratory physiotherapy as a per cent of the cost of their ICU MV bed days, with findings of 1.4 per cent in those with VAP and 1.1 per cent in those without VAP.

Further research is required to ensure that the results of the economic analysis are one of net effectiveness. As the clinical results of the study did not show a significant advantage, it may be that the direction of cost savings in outcomes, compared to respiratory physiotherapy costs, may be due to chance alone.

Chapter 6 Discussion

This two-part, prospective randomised controlled trial investigated the effect of regular prophylactic respiratory physiotherapy on the incidence of VAP, duration of MV, and length of ICU stay in adults with ABI, as compared to a control group (Part A). Secondly, subjects from Part A who developed a VAP were randomised into a treatment or control group to establish if the provision of a regimen of regular respiratory physiotherapy influenced the outcome of VAP (Part B).

This chapter begins with a discussion of aspects of study methodology that may have influenced the findings (Section 6.1). Following this, the research hypotheses and findings of Part A and Part B of the study are discussed (Section 6.2). In Section 6.2.3 the discussion focuses on the results and implications of the economic analysis undertaken. The implications for clinical practice, the limitations of the study and recommendations for future research are then discussed in Sections 6.3 to 6.5 respectively.

6.1 Study Methodology

The validity of the results of this study may have been influenced by the study design, treatment regimen, clinical stability of the subjects, control of sedation, ventilation and cough (which will influence airway clearance), the use of incidence of VAP, duration of MV and length of ICU stay as outcome measures, and the power of the study to detect a difference between the groups. These aspects of the study methodology are discussed within the following section.

6.1.1 Study design

6.1.1.a Randomisation

Equal numbers of subjects were initially achieved in the Treatment and Control Groups for Part A reflecting the success of the randomisation process. Sixteen subjects (11.1%) in Part A did not complete the study interventions as per their allocated group. The percentage of subjects not completing their allocated study interventions in the two groups was not significantly different and was within both the conventional expectations of allowing for a 10 to 15 per cent withdrawal rate, and the power calculations and sample size determination underpinning this study. There was no difference between Part A groups for the day post-admission from which these 16 subjects did not receive their allocated intervention, and data collection for these subjects continued and was analysed in accordance with an intention to treat philosophy.

Gender distribution and BMI were the only demographic variables that were not comparable between groups in Part A. The gender distribution of the Treatment Group 1 reflects the male dominance for ABI, whereas the equal number of males and females randomised to the Control Group 2 is not representative of the normal incidence rate for ABI (Fortune &

Wen 2000). However, gender has not been identified as a potential risk factor for VAP (Bauer et al. 2000; Bonten et al. 2004; Craven & Steger 1996; Torres et al. 1999), and so this chance finding is not considered to have influenced study results.

Subjects in the Treatment Group 1 had a higher mean BMI than the Control Group 2 and the mean difference of 2.1kg/m^2 between the groups is statistically and clinically significant. The BMI measures were recorded as soon as possible post-admission to ICU and due to the initial management of ABI that includes fluid resuscitation measures, the subject's weight was generally higher during the initial period in ICU than their normal pre-morbid status. However, this would have applied equally to both groups. The difference detected in mean BMI between the Treatment Group 1 and Control Group 2 may be partially explained by the gender distribution differences in the groups. Males generally have a higher BMI (normal range 20-25) than females (normal range 19-24) (Van De Graaff & Fox 1986). With Treatment Group 1 having 70.8 per cent males, the significantly higher BMI in this group may simply be reflective of the male dominance. The BMI has not been reported as a risk factor influencing the incidence of VAP per se (Bauer et al. 2000; Bonten et al. 2004; Craven & Steger 1996; Torres et al. 1999). Therefore the finding that the Treatment Group 1 had a greater BMI than the Control Group 2 is not considered as likely to influence the study results.

Therefore it was felt that the randomisation process, withdrawal rates and timing of withdrawals were unlikely to influence the study results for Part A.

The groups in Part B were equivalent with respect to demographic variables, affirming the success of the randomisation process in achieving comparable groups. However, there was a significant difference between group randomisation in Part A and subsequent group allocation in Part B. Results in Part B may have been influenced by potential carry over effect from Part A, as only nine subjects (27.3%) crossed over between the Treatment and Control Groups (from Part A to Part B).

6.1.1.b Blinding

The nature of this study did allow for blinding of the subject and their family to overcome the potential for participator bias. Medical and nursing staff were not informed that patients were in the study, or of group randomisation, in an effort to blind them and avoid any changes to their management that may have confounded the results. There was, however, no formal assessment of the success of blinding of medical and nursing staff. It was not possible to blind the physiotherapists as they were required to provide the respiratory physiotherapy interventions. However the Principal Investigator measured all outcomes of the study without informing the physiotherapists of the results. Potential bias of the Principal Investigator can not be excluded given the Principal Investigator both provided respiratory physiotherapy interventions and undertook data collection. Lack of funding and physiotherapy resources prohibited the use of a data collector blind to group allocation.

Staff within the RPH Microbiology Department responsible for processing and analysing the daily surveillance ETA samples on each subject, and the periodic NBL samples used to confirm the diagnosis of VAP on those with suspicions of VAP, were blind to subject inclusion into the study and group randomisation. As the positive diagnosis for VAP was determined by staff in the RPH Microbiology Department blinded to subject inclusion in the study, this potential source of inclusion bias for Part B was avoided.

6.1.2 Treatment regimen

There are only a limited number of studies investigating respiratory physiotherapy in ICU, these studies often described the treatment regimen inadequately, investigated non-standardised combinations of techniques, and had low statistical power. This introduces the possibility of confounding variables which may influence the outcomes obtained. In this study a structured regimen based on respiratory physiotherapy techniques, which individually were supported by scientific evidence, was used. The treatment regimen used in Part A and B of the study was clearly described with variables of application controlled where possible. However the application of the treatment regimen allowed some flexibility to meet specific subject circumstances. For example, a subject with unstable pelvic or spinal fractures did not necessarily receive the positioning component of the physiotherapy regimen. Similarly if a subject had a pneumothorax with signs suggestive of an ongoing air leak, MH is contraindicated as a physiotherapy technique (Woodard & Jones 2002; Hough 2001) and so the subject would not have received the MH component of the respiratory physiotherapy regimen for part of their time in the study. These were considered constraints reflective of normal clinical practice of respiratory physiotherapy within ICU.

The study was designed to evaluate a regimen of respiratory physiotherapy techniques that are commonly performed and reflective of standard clinical practice at RPH. The duration of each respiratory physiotherapy intervention (average of 30 minutes) was considered realistic, achievable and reflective of clinical practice. The provision of six treatments in each 24-hour period however was not reflective of standard clinical practice at RPH. The frequency of treatment chosen for this study was considered to represent a maximum level of service that would potentially be achievable in any facility. It was thought that such a high frequency of respiratory physiotherapy would provide a clear contrast to the Control Groups, with the aim of maximising the potential to detect a difference in the outcome measures. In facilities in which respiratory physiotherapy is not available 24-hours a day, 7 days a week, such a treatment regimen would not be feasible and would not reflect standard clinical practice.

Should the results of Part A or B of the study have identified a significant difference between the Treatment and Control Groups, then Part C of the study would have proceeded. The aim of Part C of the study was to establish if the frequency of respiratory physiotherapy interventions influenced the incidence and/or resolution of VAP by using groups in the study

design that reflected more closely the levels of respiratory physiotherapy in clinical practice among ICUs within Australasia. However, as the results of this study did not identify a difference in outcome between those receiving six respiratory physiotherapy interventions per day and those not receiving respiratory physiotherapy, there was no indication at this time to proceed to Part C in order to investigate outcomes arising from frequencies of respiratory physiotherapy interventions between these two extremes.

6.1.3 Clinical stability

6.1.3.a Exclusions

Subjects excluded from the study were considered to be clinically unstable and would not have normally received respiratory physiotherapy. The clinical status of the 144 subjects completing the study was considered to be reflective of patients normally receiving respiratory physiotherapy as part of usual clinical practice at RPH.

6.1.3.b Subjects not receiving allocated intervention

This study established clear and comprehensive criteria for clinical stability and processes for managing subjects who were unable to receive their allocated intervention. Reasons for subjects not receiving their allocated intervention were typical of usual scenarios encountered in clinical practice.

On average those subjects in Part A randomised to Treatment Group 1 received 4.1 respiratory physiotherapy interventions each day for the duration of their time on MV, a frequency lower than the prescribed six treatments each day. However the figure of 4.1 included all 72 subjects in Treatment Group 1, including subjects not receiving all their allocated interventions, which will have influenced this mean value. For Part B, the 17 subjects randomised to Treatment Group 3 received on average 4.5 respiratory physiotherapy interventions each day for the duration of their time on MV. Two subjects from Treatment Group 3 did not receive all their allocated intervention, which again will have influenced this mean value.

Other possible factors that impacted on the frequency of physiotherapy treatments were subject unavailability as a consequence of medical and nursing assessments and/or interventions, performance of investigations such as CT or cerebral angiography, periods in the operating theatre for neurosurgical or interventional neuro-radiological procedures (such as replacement of ICP monitoring devices or craniotomy for evacuation of mass lesions) or other trauma related procedures, or transient periods of haemodynamic or neurological instability. These factors are all common events encountered during an ICU admission following ABI, and as such reflect the normal constraints to the practice of respiratory physiotherapy. In determining the mean value of 4.1 physiotherapy treatments received per day, it is suggested that these listed factors led to the lower than prescribed frequency of physiotherapy, more so than the inclusion of subjects not receiving all their allocated

interventions in the analysis.

6.1.3.c Neurological status

Previous studies of respiratory physiotherapy in patients with ABI have reported transient changes in ICP associated with the respiratory physiotherapy interventions (Brimioulle et al. 1988; Brimioulle et al. 1997; Crosby & Parsons 1992; Ersson et al. 1990; Garradd & Bullock 1986; Imle et al. 1988; Imle et al. 1997; Paratz 1992; Paratz & Burns 1993). Whilst physiotherapists clinically monitored subjects during treatments, this study did not attempt to record ICP or CPP during respiratory physiotherapy, or to formally investigate the clinical stability of patients with ABI during respiratory physiotherapy interventions, or examine the clinical implications of any potential changes in ICP or CPP arising from the respiratory physiotherapy. These are all areas for future research.

For the purpose of this study, respiratory physiotherapy interventions were not commenced if the subject had labile ICP or CPP, a sustained ICP of greater than 25mmHg or a sustained CPP of less than 70mmHg. Labile was considered as a clinically significant alteration in the ICP or CPP of 20 per cent or more of resting values, occurring spontaneously without stimulation, which necessitated definitive intervention. Similarly, if the ICP became greater than 25mmHg or the CPP less than 70mmHg during the respiratory physiotherapy then the treating physiotherapist modified their application of the intervention to ensure clinical stability was maintained. If modification to the respiratory physiotherapy intervention did not result in the ICP and CPP limits being upheld, the treatment was ceased. However, the number of physiotherapy treatments modified or not received during this study due to neurological status was not recorded. These treatment boundaries reflect standard clinical practice at RPH, but may not reflect physiotherapy treatment limitations at other facilities. It is considered that the clear defining of boundaries for neurological variables in this study does enable repetition of the treatment regimen.

It is also worth acknowledging that neurological status was not assessed and compared between groups except using GCS at admission. Any differences in duration of MV, length of ICU stay or incidence of VAP may be due to post-admission neurological status. Re-measuring of neurological status was not undertaken as there was no easy or practicable way of re-assessing neurological status in a standardised manner due to variations in subject medical management. It is considered that neurological status post admission is a major potential confounding variable, and that incidence of VAP, duration of MV and length of ICU stay may all be primarily influenced by the severity of the ABI.

6.1.3.d Haemodynamic and respiratory status

Parameters for clinical stability of haemodynamic and respiratory status were also defined within the exclusion criteria. These parameters also served to guide the physiotherapist during the application of respiratory physiotherapy and provide a framework for when to commence, to modify or to cease the respiratory physiotherapy interventions.

As for the neurological parameters, the criteria defining haemodynamic and respiratory stability reflect standard practice in the ICU at RPH and were designed to ensure the overall clinical stability of the subjects was not compromised.

6.1.3.e Summary

No specific record was kept of the number of respiratory physiotherapy interventions not received or terminated prematurely due to issues of clinical stability. Critical incident monitoring was in-situ during the study period, with no issues being brought to the attention of the Principal Investigator for any study subject. The intent of the study design was to ensure that a structured regimen of respiratory physiotherapy was safely provided to those randomised to the Treatment Groups within the constraints of the subject's clinical status. Subjects did not receive their full quota of prescribed interventions, which is reflective of usual ICU physiotherapy practice being constrained by logistics of patient availability and clinical stability considerations.

6.1.4 Control of clinical management

During this study there were no attempts to control for facets of clinical management such as the type and level of sedation, the mode and settings of MV support, active cooling, or the frequency and intensity at which the subject coughed, either spontaneously or stimulated via a suction catheter.

The level and type of sedation, the potential use of neuromuscular blockade agents, or use of barbiturates was not recorded or controlled for in this study. Coma and chemical paralysis are risk factors for the development of VAP (Bauer et al. 2000; Bonten et al. 2004; Cook et al. 1998b; Fleming et al. 2001; Pawar et al. 2003). As such, the level of coma and use of medications to control ICP or to regulate temperature may have acted as confounders to the incidence of VAP or influenced recordings of measures of the CPIS relating to temperature. Variations in duration of medically induced coma may have also influenced the duration of MV and length of ICU stay.

The MV support strategies utilised were also not recorded or controlled for in this study. Variations in mode and settings of MV may have influenced recording of elements of the CPIS relating to oxygenation or other clinical information measures of oxygenation. Non-standardised MV support strategies may have also influenced measures of duration of MV due to variation in strategies and weaning processes.

Thermoregulation, and in particular active cooling, of the patient with ABI to a desired temperature is a commonly used strategy to control metabolic rate and therefore assist with ICP control and oxygenation (Yanko & Mitcho 2001). During this study no attempts to monitor or control the use of active cooling were made. The use of active cooling may have altered the temperature element of the CPIS and therefore potentially influenced the arousal of suspicion of VAP.

Airway clearance, either via spontaneous or stimulated cough and suction was not controlled for during this study, primarily as it would not be possible to measure or control. During the respiratory physiotherapy interventions, limits were applied to the frequency of airway suction, but no restrictions existed for airway suction outside of the respiratory physiotherapy regimen by other health care workers. Therefore in all subjects nursing and medical staff were able to undertake airway clearance via suction as they felt clinically necessary. There may have been significant variation between subjects in the frequency and intensity at which the subject coughed, either spontaneously or stimulated via a suction catheter, and therefore variation in the airway clearance achieved external to the respiratory physiotherapy regimen. Such variation may have influenced the potential for sputum retention and the possibility of VAP development, as well as the recording of the CPIS element pertaining to sputum quantity.

Use of the CPIS to arouse suspicion of VAP necessitated daily surveillance ETA samples. Results of the ETA microscopy and semi-quantitative analysis were uploaded by the RPH Microbiological Department to the RPH computing package detailing patient specific results from clinical investigations (such as haematological, microbiological, and biochemical). As the ICU medical staff were able to view subject-specific microbiological results, they were not blinded to the surveillance ETA microscopy and semi-quantitative analysis results. Access to these results may have influenced the ICU medical staff management, particularly relating to use of antibiotics. As antibiotic therapy is the mainstay of VAP management, as well as a potential preventative strategy, such alterations in management may have influenced many of the outcome and clinical measures recorded in this study.

Variation in sedation, ventilation, thermoregulation, and suction are all to be expected as part of usual clinical practice and individualised care. There is potential for this variation to confound measures recorded, but randomisation and adequate sample size should have ensured such variations were equally distributed between the groups. Future research into the influence of respiratory physiotherapy on the incidence of VAP using the CPIS could consider the concealment of results of microbiological processing of the surveillance of ETA samples from medical staff to avoid potential changes to management that may significantly confound any study findings.

6.1.5 Outcome measures

The use of the incidence of VAP (Part A), duration of MV (Part A and B) and length of ICU stay (Part A and B) as outcome measures for this study requires discussion. These outcome measures were very clearly defined, significant endpoints that are clinically and economically important. However there were numerous influences and confounders to each of these outcome measures that may render them insensitive to the effect of respiratory physiotherapy within the current sample size.

6.1.5.a Incidence of ventilator-associated pneumonia

The literature addressing the incidence, risk factors and preventative strategies for VAP makes little mention as to the role of respiratory physiotherapy. This may be because the role of respiratory physiotherapy has not been adequately investigated. Alternatively, maybe the reality within the clinical environment is that respiratory physiotherapy does not appear high on the list of options available or considered to be effective, based on clinical anecdotal experience.

The ABI population is well established as being at a higher risk for VAP, particularly those with a severe ABI (Antonelli et al. 1994; Berrouane et al. 1998; Bonten et al. 2004; Celis et al. 1988; Chevret et al. 1993; Ewig et al. 1999; Harris et al. 2000; Helling et al. 1988; Hsieh et al. 1992; Rello et al. 1992). Only those with a severe ABI as defined by a GCS less than nine were studied. It may be that the severity of the underlying neurological disorder and the overwhelming presence of risk factors may not be able to be modulated by the provision of respiratory physiotherapy. It may also be that due to the nature of ABI and its ICU management, respiratory physiotherapy is not sufficiently effectual to achieve its desired outcomes. The requirement for ICP/CPP control, minimalisation of stimuli and preference for clinical stability through the use of sedation, controlled MV and immobilisation may overshadow any potential benefits from respiratory physiotherapy in improving physiological parameters such as lung compliance and arterial oxygenation.

Within the more recent literature on VAP it is becoming apparent that no one single intervention or strategy is universally effective in preventing VAP. Current topics of deliberation are that perhaps 'bundles of care' are required in which a number of approaches are simultaneously required to target prevention of VAP (Bonten et al. 2004; McGee et al. 2004). It is postulated that a number of strategies working synergistically, as opposed to a single intervention working in isolation, may offer the best hope for modifying the incidence of VAP.

Power projections and sample size determination for this study were based on the assumption of an incidence of VAP rate of 30.0 per cent, with a desired reduction of 20.0 percentage points resultant from the application of the respiratory physiotherapy. The actual incidence of VAP recorded in this sample was 22.9 percent (19.4% in the Treatment Group 1 and 26.4% in the Control Group 2). Given that the actual incidence of VAP was lower than anticipated (and at the lower end of published rates), the ability of this variable to be responsive to change of the desired magnitude was limited.

Options to further explore the influence of respiratory physiotherapy on the incidence of VAP may include using a larger sample via a multi-centre trial, or studying respiratory physiotherapy as part of a combined package of strategies, although it is acknowledged that these strategies may introduce other confounding factors.

6.1.5.b Duration of mechanical ventilation

The decision as to when to cease MV is multifactorial, and at RPH largely determined by the Intensive Care Specialist rostered for the day. The ICU at RPH does not utilise formalised regimens for weaning from MV, and responsibility for initiating and progressing weaning is not delegated to non-medical staff. Neurological status, time of the day, clinical stability of the subject, overall ICU workload and bed availability status, neurosurgical team input, timing of sedation weaning, timing of insertion of percutaneous tracheostomy, and personal approach of the ICU Specialist are some of the many factors influencing when weaning from MV is commenced and the pace at which weaning is undertaken.

One could argue that through randomisation such factors would apply equally across all subjects in the study. However the variations of the weaning process may act as a significant confounder, which may render the duration of MV less sensitive to change as an outcome variable. The duration of MV was very variable in this study, highlighting the heterogeneity even within the sample population of subjects with ABI. Therefore it may be questioned as to whether respiratory physiotherapy could have sufficient influence on changing this variable with the current sample size, and whether a larger sample size is warranted.

6.1.5.c Length of intensive care unit stay

Similarly the decision as to when a subject can be discharged from ICU is subject to multiple influences and potential confounders, perhaps even more so than factors affecting duration of MV. Length of ICU stay for a subject is influenced by the subject and their neurological status, overall clinical status, ICU specific factors such as workload, bed availability, and staffing, as well as factors external to the ICU such as discharge destination and bed availability, ward staffing and case-mix, infection control constraints, and neurosurgical team input and preferences. Preference in management of the Intensive Care Specialist rostered for the day, day of the week, and time of the day are other factors that anecdotally influence when a subject is discharged from ICU, and therefore the determination of the length of ICU stay variable.

Again it can be argued that with randomisation such issues would be equally distributed between the groups. As for duration of MV, the length of ICU stay was also very variable, highlighting the heterogeneity within the sample population. The responsiveness and sensitivity to change with this variable resultant from respiratory physiotherapy may be questionable.

6.1.5.d Summary

For this study, pursuit of clinically relevant outcomes necessitated the choice of outcome measures such as incidence of VAP, duration of MV, and length of ICU stay despite the possibility that use of such outcome measures may be questioned. It is acknowledged that such outcome measures may possibly not have been responsive or sensitive to change from respiratory physiotherapy treatment. However it is also acknowledged that a documented

effect size for respiratory physiotherapy in the ABI population has yet to be determined.

When looking at the 'big picture' it is necessary to look beyond physiological endpoints. A regimen of respiratory physiotherapy may well in fact improve lung compliance and arterial oxygenation (Berney & Denehy 2002; Hodgson et al. 2000; Jones et al. 1992b; Patman et al. 2000), but if such physiological enhancements are not translated to tangible benefits in subject outcomes, then the clinical relevance of findings are questionable. Then there is a question of costs and the economic imperatives within the modern healthcare environment that dictate that interventions need to consider cost evaluation. Physiological endpoints as opposed to clinical milestones are less relevant to the subject and to the healthcare system that finances the intervention. The challenge in engaging in meaningful evidence based practice lies in pursuing outcomes that can be shown to be of clinical and potential economic benefit to the individual subject and to the wider healthcare system.

6.1.6 Statistical power

6.1.6.a Part A

It was not possible to directly the estimate effect size for this study due to the lack of published data as to the effectiveness of respiratory physiotherapy for the ABI population. Therefore some assumptions were required, including that the incidence of VAP for the Control Group population would be precisely 30.0 per cent and that changes of actual percentage points of less than 20.0 were not clinically significant. The power of this study was 80 per cent thus allowing reasonable confidence that there is no difference between the Treatment and Control Groups, assuming a clinically significant difference of at least 20 per cent in the incidence of VAP.

6.1.6.b Part B

In Part B of the study, assuming a theoretical large effect size that represented a clinically significant difference between mean duration of MV of at least one standard deviation between the groups, the power was to be 80 per cent with 17 subjects per group. However, as a consequence of the protracted data collection phase of Part A, and the lower than anticipated incidence of VAP, the study was ceased after 44 months. At the time of study cessation 33 subjects had been enrolled in Part B. Consequently this part of the study is slightly underpowered, thus limiting the confidence to reasonably conclude that there is no difference between the Part B Treatment and Control Groups for the mean duration of MV.

6.2 Research Findings

This section of the Discussion outlines the key findings of this research within the headings of Part A, Part B and Economic Analysis. Findings are discussed in terms of the primary outcome measures of incidence of VAP, duration of MV, and length of ICU stay.

The number of patients with ABI and fulfilling study inclusion criteria during the data collection period was 193, of which 144 (74.6%) were enrolled. All eligible patients not

included in the study were accounted for with recording of appropriate exclusion criteria or non-consent reasons for not being enrolled. Thus, this study enrolled all available patients during the data collection period and potential concerns of selection bias would be unfounded.

6.2.1 Part A

Based on a review of the literature it was hypothesised prior to commencing this study that the provision of prophylactic respiratory physiotherapy, in addition to routine medical and nursing care, to the ABI patient population in the ICU would significantly decrease the incidence of VAP. It was also hypothesised that a respiratory physiotherapy service provided in the ICU would significantly influence ABI patient outcomes, such as the duration of MV and length of ICU stay. The findings of this study indicate that the use of a regular prophylactic respiratory physiotherapy regimen, repeated six times per day and comprised of positioning, MH and suctioning does not appear to prevent VAP, reduce length of ventilation or ICU stay in adults with ABI.

6.2.1.a Incidence of ventilator-associated pneumonia

Of the 144 subjects included in the study, 33 satisfied the criteria for the diagnosis of VAP, representing 22.9 per cent of the study population; 14 subjects (19.4%) from Treatment Group 1 and 19 (26.4%) from Control Group 2. No significant difference between groups was detected for the incidence of VAP. This incidence of VAP at RPH is at the lower end of that previously published, particularly in the ABI population (A report from the NNIS System 2003; George 1995; Sirvent et al. 2000).

Respiratory physiotherapy does not specifically address or target the identified causes or risk factors for VAP, with the exception of avoidance of the supine position. Preceding the commencement of physiotherapy are a number of factors or events potentially responsible for commencing the cascade of pathogenesis for VAP. Presence of premorbid risk factors such as age and smoking, the initial severity of illness associated with the ABI, endotracheal intubation, aspiration either at the time of the ABI or ETT insertion, and the presence of coma are all features that occur prior to, and are unable to be influenced by, the provision of physiotherapy in ICU. Physiologically the prophylactic respiratory physiotherapy may assist with airway clearance, improving oxygenation and lung compliance, but if the lower respiratory tract has already been compromised with bacteria and an inflammatory response is already occurring, then this may explain why the incidence of VAP was not altered by the physiotherapy.

Only two related articles in which respiratory physiotherapy and incidence of VAP were investigated have been identified, those of Ntoumenopoulos et al (1998; 2002). The findings of this study are consistent with those of Ntoumenopoulos et al (1998), who also failed to demonstrate a significant relationship between respiratory physiotherapy and the incidence of VAP. In their study of 46 trauma patients, twice daily respiratory physiotherapy involving

MH, GADP and suction was not associated with a reduced incidence of VAP (Ntoumenopoulos et al. 1998); however patients with ABI were excluded thereby limiting comparison to this present study. Comparison with the current study is also limited due to the lack of reporting by Ntoumenopoulos et al (1998) of demographic characteristics such as gender, history of smoking or COPD, and the significantly lower APACHE II scores (means of 12.3 and 14.1) in their subjects as compared to this study. Notably these low mean APACHE II scores are less than the threshold score of 16 which has been shown to be a risk factor for VAP (Chevret et al. 1993), suggesting the population studied by Ntoumenopoulos et al (1998) was not at a high risk of VAP and therefore less likely to demonstrate changes in the incidence of VAP as a result of respiratory physiotherapy. Further limitations to the study of Ntoumenopoulos et al (1998) included the small sample size (n=46) and power of 0.21 (Crowe et al. 2003), the use of non-specific clinical criteria for VAP diagnosis, and the early withdrawal of subjects with a suspicion of VAP who went on to receive more intensive respiratory physiotherapy.

Findings of this current study contrast with a more recent study by Ntoumenopoulos et al (2002) in which it was reported that twice daily respiratory physiotherapy comprising GADP, vibration and suction was independently associated with a reduction in VAP. In their study of 60 adults, of whom 26.7 per cent had ABI, the authors reported an incidence of VAP of 39 per cent in the control group and eight per cent in the respiratory physiotherapy group (Ntoumenopoulos et al. 2002). The heterogeneity of their study population (general medical, surgical, and/or trauma patients) (Ntoumenopoulos et al. 2002) may account for the different response to respiratory physiotherapy, although specific admission diagnoses and subgroup results were not reported. Additionally in the present study the subjects with ABI were younger, had worse APACHE II scores, fewer had a history of COPD, and had a much lower incidence of lung collapse than the subjects of Ntoumenopoulos el al (2002). Again this variation in demographic characteristics may have contributed to the contrasting findings obtained, as age, severity of illness and history of COPD are all risk factors for VAP (Bauer et al. 2000; Bonten et al. 2004; Craven & Steger 1996; Torres et al. 1999) and subjects with lung collapse are likely to be more responsive to respiratory physiotherapy (Stiller et al. 1990; Stiller et al. 1996).

Season of the year has been independently associated with the development of VAP (Craven et al. 1986; Bauer et al. 2000). Seasonal variations in pathogen susceptibility should not have been a confounding factor influencing the incidence of VAP in this present study as it was conducted over a period of 44 months. Similarly the study of Ntoumenopoulos et al (1998) was conducted over a 17 month period. However the results reported by Ntoumenopoulos et al (2002) were obtained over a six month period which did not encompass the traditional winter season, and this may have influenced pathogen susceptibility, incidence of VAP and subject responsiveness to intervention.

A study by Hall et al (1996) is incorrectly cited in the VAP literature to argue that respiratory physiotherapy is not an effective strategy to prevent VAP (Kollef 1999a; Lustbader et al. 2001). However this study by Hall et al (1996) examined the prevention of respiratory complications following upper abdominal surgery using respiratory physiotherapy versus incentive spirometry in extubated patients on a surgical ward, as opposed to intubated patients within ICU with VAP as an outcome measure.

A meta-analysis (involving 18 trials) of the effectiveness of respiratory physiotherapy in ICU found that respiratory physiotherapy did not prevent pneumonia (Devroey et al. 2002). Similarly no significant difference in incidence of VAP or timing of onset of VAP following twice daily respiratory physiotherapy involving GAPD and forced expiratory techniques in a study of 22 subjects receiving MV for greater than 48 hours in a general ICU has been reported (Norrenberg et al. 2004). However this information from Devroey et al (2002) and Norrenberg et al (2004) is only presented in abstract form and thus further exploration of the respiratory physiotherapy techniques studied and critique of the findings is not possible.

6.2.1.b Duration of mechanical ventilation

The difference of 33.5 hours between the mean duration of MV of the Groups found in this study was not statistically significant, mainly due to the large variance evident in the data. Even when considering the median values for duration of MV a similar picture emerges with a non-significant difference of 18.4 hours found.

Physiologically, respiratory physiotherapy may improve airway clearance, lung compliance and arterial oxygenation in intubated patients (Denehy 1999; Berney & Denehy 2002; Berney et al. 2004; Hodgson et al. 2000; Jones et al. 1992b; Patman et al. 2000; Stiller et al. 1996). Any physiological improvements in lung compliance or oxygenation that may have resulted from physiotherapy did not translate to changes in clinical endpoints such as the incidence of VAP, duration of MV, or length of ICU stay in this study. Reasons why physiological improvements occur following physiotherapy but not alterations in duration of MV may be related to the short term nature of any physiological changes, to a potential dosage response from the physiotherapy, or due to the competing influence of confounders such as sedation levels and ongoing coma, mode of MV, or the ongoing pathogenic process of VAP. Alternatively it could be considered that respiratory physiotherapy improves 'signs and symptoms' by assisting with airway clearance and re-expansion of atelectasis, but does not treat the cause of increased sputum, atelectasis, or the infective process, which is why clinical endpoints are unaltered by physiotherapy. If there are no 'signs and symptoms' to treat, as was the case with a significant number of the ABI subjects studied, then it is unlikely that prophylactic respiratory physiotherapy will have sufficient scope to improve physiological variables to the degree that alterations in clinical endpoints are evident.

The findings of this study are consistent with Ntoumenopoulos el al (1998) and Ntoumenopoulos el al (2002), who also failed to demonstrate any changes in duration of MV

in their populations following respiratory physiotherapy. The mean duration of MV in the present study of 7.2 and 8.6 days in the Treatment and Control Groups respectively is longer than in the groups of Ntoumenopoulos el al (1998) (6.1 and 5.2 days) and the median data presented by Ntoumenopoulos el al (2002) (4.4 and 5.2 days). The variation in duration of MV between the studies may be related to the nature of the patient population studied, or the higher APACHE II scores, signifying more acutely unwell subjects, in the current study.

Results from these studies could be interpreted in one of three ways. The provision of respiratory physiotherapy may have no effect on duration of MV or duration of MV may be an inappropriate outcome measure. Alternatively the large variation evident in the reported data, whether in a heterogeneous or homogonous sample population, may signify that a larger sample size may be required to identify significant changes in duration of MV resulting from the use of respiratory physiotherapy. Future, possibly multi-centred, research of respiratory physiotherapy with power and sample size determination based on desired changes in duration of MV is warranted.

6.2.1.c Length of intensive care unit stay

In this study a similar picture to duration of MV was evident for results obtained for length of ICU stay. An apparent 32 hour difference in mean length of ICU stay favouring the Treatment Group 1 was found, but again these data showed a wide variance, and no statistical difference between Groups was noted.

The results of this study replicate those of Ntoumenopoulos el al (1998) and Ntoumenopoulos el al (2002), who also failed to detect any changes in length of ICU stay based on receipt of respiratory physiotherapy. The mean length of ICU stay in this present study of 9.3 and 10.7 days in the Treatment and Control Groups respectively is longer than in the groups of Ntoumenopoulos el al (1998) (7.4 and 6.8 days) and the median data presented by Ntoumenopoulos el al (2002) (5.8 and 5.6 days). As for duration of MV, explanations for this variation in length of ICU stay may be related to the differing severity of illness, as reflected by the APACHE II score, the longer duration of MV reported, or related to the differing subject populations studied.

Results pertaining to length of ICU stay from these studies could also be interpreted in one of three ways. The provision of respiratory physiotherapy may have no effect on length of ICU stay or length of ICU stay may be an inappropriate outcome measure. Alternatively the large variability in the reported data, whether in a heterogeneous or homogonous sample population, may signify that a larger sample size may be required to identify significant changes in length of ICU stay resulting from the use of respiratory physiotherapy. As the cost of an ICU bed day is significant, future research endeavours should focus on the ability of respiratory physiotherapy to affect length of ICU stay.

6.2.2 Part B

It was hypothesised that the provision of respiratory physiotherapy to those with VAP within the ABI patient population would significantly assist in the resolution of VAP, leading to improved patient outcomes such as reduced duration of MV and length of ICU stay. The respiratory physiotherapy regimen in Part B was identical to that in Part A of the study. The findings of Part B indicate that in adult ABI subjects with VAP, use of a regular respiratory physiotherapy regimen, repeated six times per day and comprising of positioning, MH and suctioning did not expedite recovery in terms of reducing the duration of MV or length of ICU stay.

Thirty-three subjects (22.9%) from Part A of the study satisfied criteria for the diagnosis of VAP, and were transferred to Part B and re-randomised, 17 to the Treatment Group 3 and 16 to the Control Group 4. The Groups in Part B of the study were comparable with respect to demographic variables and on day post-admission for diagnosis of VAP.

6.2.2.a Duration of mechanical ventilation

The difference of nine hours in duration of MV, favouring the Treatment Group 3, was neither statistically or clinically significant. A large variance was evident in the duration of MV data in Part B, similar to that in Part A. As duration of MV is a significant risk factor for VAP (Bauer et al. 2000), it may be argued that any reduction in duration of MV should be considered clinically significant. However, as subjects in Part B already had a VAP, a threshold for reduction in duration of MV considered clinically significant was based more on economic grounds. A 12 hour difference in duration of MV was considered to have an influence on ICU nursing staff to patient ratios and discharge planning within the ICU at RPH, and therefore representative of clinical significance.

No previous studies investigating the influence of respiratory physiotherapy on the duration of MV in subjects with VAP were identified. The inability to demonstrate a significant relationship between respiratory physiotherapy and duration of MV in subjects with VAP in this study may be due to the lower than desired subject numbers in Part B of the study, influencing statistical power. Another possibility for the results obtained could relate to the fact that there were only nine subjects that crossed over between the Treatment and Control Groups (from Part A to Part B). The potential carry over effect from Part A which may have influenced results in Part B is worthy of further focussed investigation. The influence of external factors or confounders may also have contributed to the result obtained. Finally it must be contemplated that respiratory physiotherapy may not have influenced duration of MV in ABI subjects with VAP.

In this study, subjects with VAP had a mean duration of MV of 15.2 days, as compared to 6.0 days in those without VAP, representing a mean difference of 9.2 days which is significantly different. Results of this present study affirm previous results that the mean duration of MV is increased from 5.0 to in excess of 22.0 days in those with VAP as compared to those without

VAP (Cook et al. 1998a; Dietrich et al. 2002; Jimenez et al. 1989; Rodriguez et al. 1991).

6.2.2.b Length of intensive care unit stay

Results of Part B of the study for mean length of ICU stay mirror those of duration of MV. An apparent 13 hour difference in mean length of ICU stay in favour of the Treatment Group 3 was evident, but again these data show a wide variance and no statistical difference was found.

No previous studies were identified in which the influence of respiratory physiotherapy on the length of ICU stay in subjects with VAP was studied. As for duration of MV, the inability to demonstrate a significant relationship between respiratory physiotherapy and length of ICU in subjects with VAP in this study may be due to the low subject numbers in Part B of the study, the influence of confounders, or because no benefit from respiratory physiotherapy exists. Again further focussed investigation on the potential carry over effect from Part A, which may have influenced length of ICU stay in Part B, is warranted.

In this study subjects with VAP had a mean length of ICU stay of 16.3 days, as compared to 8.1 days in those without VAP, a mean difference of greater than eight days which is significantly different. Results of this present study affirm previous results that the increased length of ICU stay attributable to VAP is between 4.0 and 21.0 days (Bercault & Boulain 2001; Cook 2000; Dietrich et al. 2002; Heyland et al. 1999; Rodriguez et al. 1991).

6.2.3 Economic analysis

By conducting an economic analysis including a detailed cost analysis of the intervention, this study has provided the first description of the financial costs of respiratory physiotherapy time in providing interventions to patients with ABI in ICU. No previous studies have been identified that report the costs of physiotherapy for any ICU patient population.

It was hypothesised that there would be a cost saving associated with providing respiratory physiotherapy to patients with ABI in the ICU. However, no statistically significant differences were detected on the clinical outcomes of incidence of VAP, duration of MV or length of ICU stay, and so it was not possible to determine any formal cost savings or reliable cost effectiveness ratios resulting from prophylactic respiratory physiotherapy in subjects with ABI. However as outlined in the following paragraphs, the possible cost savings to the ICU, as compared to costs of respiratory physiotherapy, are potentially large. Despite statistically significant differences not being detected, there was a trend towards improvement in the outcome measures favouring the Treatment Group. Therefore, it is suggested that in light of the comparatively minimal cost associated with providing respiratory physiotherapy, it may be a worthwhile investment to continue to provide prophylactic respiratory physiotherapy to subjects with ABI who have not developed VAP. Further research is required to ascertain the effectiveness of respiratory physiotherapy in reducing the incidence of VAP, duration of MV or length of ICU stay.

6.2.3.a Incidence of ventilator-associated pneumonia

Data from the economic analysis determined that for each subject with ABI receiving a prophylactic regimen of respiratory physiotherapy in ICU for their entire duration of MV, in an attempt to prevent VAP, the average cost of physiotherapy was $487.

Based on ICU MV bed days, an incremental health cost of $35,950 per episode of VAP was found. So, despite no statistically significant differences in incidence of VAP being evident, it may be considered that a regimen of physiotherapy at a cost of $487 is money well spent in pursuit of a potential cost saving of $35,950 per VAP case prevented. Based on these figures, 74 subjects with ABI would need to be prophylactically treated before the costs of physiotherapy outweighed the savings from one VAP case prevented.

6.2.3.b Duration of mechanical ventilation

Whilst no statistically significant difference in duration of MV was found with the provision of respiratory physiotherapy in Part A, there was a positive finding of a reduction of 33.5 hours favouring the Treatment Group. This reduction in duration of MV is equivalent to $5,758 of ICU bed day costs and represents 17.2 per cent of the total average ICU MV bed day cost for the period of MV. In comparison, spending $487 on physiotherapy may be considered worthwhile to pursue the estimated savings associated with a reduced duration of MV. Twelve subjects with ABI would need to be treated before the costs of prophylactic physiotherapy outweighed the savings from the reduced duration of MV in one subject.

Regular respiratory physiotherapy in subjects with VAP did not appear to expedite recovery, with only a difference of nine hours in duration of MV recorded, favouring the Treatment Group 3. In subjects who developed VAP, a regimen of respiratory physiotherapy for the remaining duration of MV following diagnosis of VAP was $788. Comparatively the average ICU bed day cost for Part B subjects was $43,865. This reduction in duration of MV is equivalent to $1,547 worth of ICU bed day costs and represents only 3.5 per cent of the total average ICU bed day cost for the period of MV in those with VAP. Comparatively the cost of respiratory physiotherapy in those with VAP would not appear to be justified in attempts to reduce the duration of MV.

However, the cost analysis of those with VAP, based on Part A group allocation, found an increased ICU MV bed day cost of $17,952 per subject from Control Group 2, as compared to those from Treatment Group 1. So, despite no statistically significant differences in incidence of VAP being found, from the comparison of costs with outcomes it appears there is a 35 per cent higher ICU MV bed day cost per subject in those with VAP that did not receive a regimen of prophylactic respiratory physiotherapy as compared to subjects that did receive physiotherapy. As only three subjects from Part A Treatment Group 1 with VAP crossed over to the Control Group 3 in Part B, this finding could be construed as there being a cumulative or carry over effect of receiving prophylactic physiotherapy prior to the diagnosis of VAP in reducing ICU MV bed day costs. Further investigation into the potential

cumulative or carry over effect of receiving prophylactic physiotherapy on costs, with a more proportionate distribution of subjects' crossing over between treatment and control groups than evident in this study, is warranted.

6.2.3.c Length of intensive care unit stay

A non-statistically significant reduction in length of ICU stay of 32.2 hours favouring the Part A Treatment Group 1 was found. This difference in length of ICU stay is of similar magnitude as the differences in duration of MV between groups. It could be interpreted that the reduction in duration of MV from respiratory physiotherapy confers no additional clinical or cost benefits in further reducing length of ICU stay. That is, differences seen in length of ICU stay are reflective of the reduction in duration of MV alone. The reduction in length of ICU stay equates to a difference of $5,534 in ICU bed day costs, which is comparable to the difference in costs associated with reduced duration of MV.

With length of ICU stay a 13 hour difference in favour of the Part B Treatment Group 3 was noted, but as for Part A, this difference was not statistically significant. Similarly the difference in Part B mean length of ICU stay mirrors the difference between groups in duration of MV. A mean difference in ICU bed day costs of $2,234 is associated with the non-significant difference in length of ICU stay between Part B groups.

It is suggested that any potential cost savings arising from respiratory physiotherapy may result from reductions in duration of MV. As there is no additional benefit from respiratory physiotherapy in reducing length of ICU stay, there does not appear to be any significant supplementary cost savings available other than via a reduction in duration of MV.

6.3 Implications for Clinical Practice

This section summarises the clinical implications arising from this study, along with generalisations and significance of the findings.

The first description of the financial costs of respiratory physiotherapy time in providing interventions to patients with ABI in ICU has been provided in this study. Such description of the costs of respiratory physiotherapy in ICU allows a clear appreciation of the human resource expenses for a particular physiotherapy regimen within an ICU population. These findings have important implications for physiotherapy service planning and budgeting within the ICU, allow comparison of respiratory physiotherapy and other interventions for this patient population, and provide a benchmark to allow other facilities to compare the costs of their clinical practice.

Subjects with a VAP were significantly younger, were admitted with a lower GCS, and more likely to have been admitted with a chest injury compared to subjects without a VAP. Duration of MV and length of ICU stay were significantly increased in subjects with VAP. Additionally it was determined that the incidence of VAP in adults with ABI in the ICU at RPH is 22.9 per cent, with an associated incremental health cost of $35,950 per episode of VAP.

The implication of these findings on clinical practice ranges from impacts on budgeting and resource allocation, knowledge of resource utilisation, benchmarking, and infection control practices for those admitted with ABI.

Use of a regular prophylactic respiratory physiotherapy regimen, repeated six times per day and comprising of positioning, MH and suctioning does not appear to prevent VAP, reduce duration of MV or length of ICU stay in adults with ABI. For subjects with ABI receiving this regimen of physiotherapy in ICU (for their entire duration of MV), in an attempt to prevent VAP, the financial cost of physiotherapy time was, on average, $487. Comparatively the ICU bed day cost for the period of MV was, on average, $33,380. Therefore respiratory physiotherapy represents 1.7 per cent of the total ICU MV bed day costs, signifying that physiotherapy represents a very minor cost within the ABI population in ICU.

In adult ABI subjects with VAP, use of a regular respiratory physiotherapy regimen, repeated six times per day and comprising of positioning, MH and suctioning does not expedite recovery in terms of reducing length of MV or ICU stay. In subjects with ABI in which VAP developed, the regimen of respiratory physiotherapy for the remaining duration of MV following diagnosis of VAP costed, on average, $788. Comparatively the ICU bed day cost for the period of MV was $43,865. Even in the presence of VAP, respiratory physiotherapy represents only 1.8 per cent of the total ICU MV bed day costs, again signifying that physiotherapy represents a very minor cost within the ABI population in ICU.

On statistical results alone it would appear that there is no role within clinical practice for the respiratory physiotherapy regimen utilised in this study for subjects with ABI. However, despite the failure to demonstrate a significant relationship between respiratory physiotherapy and the incidence of VAP, duration of MV or length of ICU stay, there may be economic grounds to consider the application of a respiratory physiotherapy regimen as part of clinical practice to prevent VAP and reduce duration of MV in adults admitted to ICU with ABI. As there is a trend towards improvement in the outcome measures favouring the Treatment Group, and the cost of respiratory physiotherapy relative to the incremental health costs per episode of VAP are minimal, there may be justification for clinical practice to include respiratory physiotherapy until these results are confirmed.

6.4 Limitations of the Study

This section outlines explanations for identified limitations of this study which may affect the validity of its findings and the ability to be make generalisations. Suggestions for necessary controls to avoid such limitations in future studies are discussed.

In any study investigating VAP there are issues relating to the method used for the diagnosis of VAP, given the absence of a gold standard method. The method chosen to diagnose VAP in this study was based on structured but easily obtainable clinical criteria in the form of the systematic CPIS surveillance to arouse suspicions of VAP, and then use of NBL to confirm

VAP. The use of the CPIS and NBL were not cumbersome, were able to be performed by physiotherapists, avoided specialised equipment and involvement of additional staff and the associated costs. Blinding of the RPH Microbiology staff processing and analysing the NBL samples was considered a positive factor that may have outweighed potential concerns or limitations associated with use of this diagnostic strategy.

A major limitation to this study was the possibility that the outcome measures may have been insensitive to change resulting from respiratory physiotherapy. The presence of potential confounding factors may have limited the responsiveness of these outcome measures, thereby limiting the ability of this study to achieve its desired aim with the current sample size. Certainly the sample size of Part B was less than projected, creating a limitation in the interpretation of Part B findings. Similarly the inability to assess neurological status in a standardised manner post admission, due to difference in medical management such as operative interventions or sedation levels, was a limitation to determining if severity of the ABI and subsequent neurological status affected study outcomes.

A number of external influences contributed to the service provision and workload in the RPH ICU, which in turn limited subject availability and recruitment rates throughout the duration of the study. The Bali bombings of October 2002 significantly impacted on the ICU case-mix for at least two months. The ICU experienced a number of endemic nosocomial pathogens (such as *vancomycin-resistant Enterococcus*, *methicillin-resistant Staphylococcus aureus*, *multi-resistant Pseudomonas aeruginosa,* and *Norovirus*) resulting in significant alterations in case management, case-mix and prolonged bed closures. Structural reforms within the Health Department of WA also impacted on the distribution of neurosurgery services within the tertiary hospitals, including RPH, which again influenced admission of ABI patients to the ICU. Finally, a major protracted structural renovation within the ICU resulted in a significant period of bed closures which influenced bed availability and case-mix from which the sample population of ABI was to be drawn. Individually each of these events may not have been a significant limitation to this study, but in combination they resulted in a noteworthy disruption to ICU admissions and management, which in turn influenced subject recruitment, and may have impacted on outcome measures such as length of ICU stay.

Results of this study are confined to adults admitted with a severe ABI, which limits the generalisation of findings to other patient populations encountered in the ICU. Risk factors for VAP are not necessarily distributed equally among various patient groups, and the few studies of respiratory physiotherapy and VAP in non-ABI populations have reported results that differ to the findings of this study. Even with this homogenous ABI sample population there was significant variance evident in the data obtained, thereby influencing internal validity. As this study was examining the cause-and-effect relationship of respiratory physiotherapy and the incidence of VAP, duration of MV and length of ICU stay, the reducing of internal validity through sample variability creates a limitation to the results reported.

One significant factor that may limit the external validity of the study findings was the frequency of the respiratory physiotherapy. The respiratory physiotherapy treatment was provided over the full 24-hour period, seven days per week which required an around-the–clock physiotherapy service provision. Six respiratory physiotherapy treatments per 24-hour period were intended, and although the average number of daily treatments received by subjects was four, this level of intervention may not be achievable in other facilities. Limitations in staff availability, rostering logistics, case-mix and workload considerations, and budgetary constraints are all potential factors limiting the repeatability of this respiratory physiotherapy regimen in other centres.

Whilst the Control Groups in this study did not receive respiratory physiotherapy, a physiotherapist still attended the bedside of Control Group subjects regularly to assess the subject and to attempt to blind nursing staff as to the group randomisation. The frequency at which Control Group subjects were reviewed was not standardised. All subjects continued to receive daily assessment of passive joint range of movement and neurological rehabilitation activities as required, as per standard clinical practice. This raises the question as to whether the Control Group subjects were true controls. The inclusion benefit of being in a clinical trial, despite being randomised to a Control Group, is a phenomena that may have influenced subject outcomes in this study, leading to potential underestimations of the value of the respiratory physiotherapy and therefore creating a limitation to the study and its findings (Lantos 1999; Parshuram & Kavanagh 2004). Future studies should consider the standardisation of assessment and input to control groups, along with monitoring strategies, to avoid any potential biases of staff that may influence inclusion benefits from manifesting.

The extensive period of data collection may have introduced confounding factors limiting this study. The timeframe of data collection in this study was 44 months during which many staff changes occurred within all ICU staff disciplines, including physiotherapy. There was no controlling for changes in ICU medical and nursing practices, medication utilisation, infection control procedures, changes in equipment, or other factors that may have in some way potentially modified the risk factor profile of the subjects for VAP, or influenced duration of MV and length of ICU stay. Such temporal changes are not thought to be a significant limitation to this study, as it is considered that randomisation would have ensured that both groups were potentially affected in similar fashion. Further studies of a multi-centred nature would reduce data collection periods to avoid this potential study limitation, but may introduce other potential confounding variables.

Finally the impact of physiotherapy rehabilitation activities in ICU on the outcome measures was not assessed. Changes in posture and exercise therapy associated with neurological rehabilitation activities undertaken by the physiotherapist in the subjects with ABI may have influenced oxygenation, airway clearance and lung volumes. In addition to desired enhancements to neurological or musculoskeletal function, the rehabilitation activities may

have also influenced cardiorespiratory status, which in term may have acted to confound the outcome measures. The lack of controlling of physiotherapy rehabilitation activities and their effects may be a limitation to this study. However, as these rehabilitation interventions were applied across all groups it is considered that this potential limitation is not a major confounder to the findings obtained. Any future studies may benefit from firstly standardising the level and timing of rehabilitation activities, and secondly investigating the influence of physiotherapy rehabilitation interventions on outcome measures such as incidence of VAP, duration of MV and length of ICU stay.

6.5 Recommendations for Future Research

This final section of the Discussion details recommendations for future research endeavours pertaining to respiratory physiotherapy in ICU and VAP.

The aim of this study was to investigate the effects of a respiratory physiotherapy regimen involving six treatments per day. However results of this current study revealed subjects only received, on average, 4.1 treatments per day in Part A, and 4.6 per day in Part B. As the frequency of physiotherapy has been shown to influence responsiveness to treatment in ICU patients with lobar collapse (Stiller et al. 1996), it is recommended that a future study be conducted to investigate higher daily frequencies of respiratory physiotherapy to establish if there is a dosage threshold that may result in significant changes to the incidence of VAP, duration of MV and length of ICU stay in subjects with ABI.

It is recommended that any future study examining the effects of respiratory physiotherapy on the incidence of VAP, duration of MV and length of ICU stay should consider the merits of utilising a multi-centre approach in the study design. This may assist with attaining obtaining a sufficiently large sample size to counter potential effects of confounders to the outcome measures, to achieve desired power, to decrease the duration of the data collection period, and to increase the external validity of any findings.

Investigation into the potential use of alternative outcome measures to those used in this current study is recommended. Collection of physiological data during the respiratory physiotherapy intervention, as well use of clinical endpoints such as those used in this study, is suggested. In order to show that no harm is done by the intervention and determine the physiological benefits arising from the respiratory physiotherapy, it is recommended that future studies gather information as to changes in neurological variables such as ICP, CPP and arousal states, in cardiovascular variables such as HR, BP and support requirements, and to respiratory variables such as respiratory support requirements, respiratory rate, SpO_2, and PaO_2/FiO_2 ratio. Linking of physiological changes to clinical endpoints arising from provision of respiratory physiotherapy could then be investigated in subsequent studies.

In any future study utilising the CPIS or NBL as part of the diagnostic strategy for VAP it is recommended to investigate blinding of ICU clinical staff to ETA and NBL microbiological

analysis results. This may eliminate any potential changes to medical or nursing management that may result from knowledge of surveillance data collected as part of the study. It is also recommended that the success of measures to blind medical and nursing staff to group allocation be investigated.

The combining of a respiratory physiotherapy regimen with other standardised strategies as part of a 'bundle of interventions' to decrease the incidence of VAP is recommended for future research. The effect of a combination of respiratory physiotherapy with other interventions on outcome measures such as duration of MV is also worthy of further investigation. Similarly, further investigation into the potential cumulative or carry over effect of receiving prophylactic physiotherapy, with a more proportionate distribution of subjects' crossing over between treatment and control groups than evident in this study, is warranted.

As this is first time such respiratory physiotherapy cost data are available, confirmation of the cost analysis results through further study in other facilities and settings is warranted. It is also recommended that costs of respiratory physiotherapy in other ICU patient populations be determined.

Conduct of a meta-analysis of existing studies that have investigated respiratory physiotherapy on outcomes such as the incidence of VAP, duration of MV and length of ICU stay may also be worthy of consideration. Finally, it is recommended that future research investigate the influence of respiratory physiotherapy in other ICU patient groups to establish if results from this study of subjects with ABI are reflective of the wider ICU population.

Chapter 7 Conclusions

This two-part, prospective randomised controlled trial investigated the effect of regular prophylactic respiratory physiotherapy on the incidence of VAP, duration of MV, and length of ICU stay in adults with ABI, as compared to a Control Group (Part A). The second part of the study (Part B) randomised those subjects from Part A who fulfilled the criteria for VAP into a Treatment or Control Group to establish if the provision of a regimen of regular respiratory physiotherapy influenced the outcome of VAP. This study also aimed to provide the first economic evaluation of the cost effectiveness of respiratory physiotherapy services for patients admitted to the ICU with ABI in decreasing the incidence of VAP and other important clinical outcomes, such as duration of MV and length of ICU stay.

The main conclusion from Part A of this study was that the use of a regular prophylactic respiratory physiotherapy regimen comprising of positioning, MH and suctioning, in addition to routine medical and nursing care, does not appear to prevent VAP, reduce duration of MV or length of ICU stay in adults with ABI. Within the ICU at RPH, the incidence of VAP in adults with ABI was 22.9 per cent, which is at the lower end of previously published incidence rates. For patients with ABI receiving this prophylactic regimen of respiratory physiotherapy in ICU (six times per day for their entire duration of MV), in an attempt to prevent VAP, the cost of physiotherapy was $487 per subject. Comparatively the ICU MV bed day cost for the period of MV was $33,380 per subject. The cost of Part A respiratory physiotherapy time for Treatment Group 1 was 1.7 per cent of the cost of their ICU MV bed days. Whilst statistically significant results were not found with clinical variables, it is suggested that the provision of a prophylactic respiratory physiotherapy regimen costing $487 per subject is a worthwhile investment in attempts to avoid the incremental health cost of $35,950 per episode of VAP.

Furthermore, in those ABI subjects with VAP, regular respiratory physiotherapy does not expedite recovery in terms of reducing length of ventilation or ICU stay. In those patients with ABI in which VAP developed, the regimen of respiratory physiotherapy six times per day for the remaining duration of MV following diagnosis of VAP was costed, on average, at $788. Comparatively the ICU bed day cost for the period of MV was $43,865. The cost of Part B respiratory physiotherapy time for Treatment Group 3 was 1.8 per cent of the cost of their ICU MV bed days. It is concluded that the cost of respiratory physiotherapy in those with VAP would not appear to be justified in attempts to reduce the duration of MV.

Compared to subjects without a VAP, those subjects with a VAP were significantly younger, were admitted with a lower GCS and more likely to have been admitted with a chest injury. Duration of MV and length of ICU stay were significantly increased in subjects with VAP, but length of hospital stay was not significantly different. Significant differences in the costs of respiratory physiotherapy and ICU MV bed day costs were evident between those subjects

with VAP as compared to those without VAP. For patients with VAP, the respiratory physiotherapy time cost was $1,029 per subject, compared to $510 for non-VAP patients. The ICU MV bed day cost for patients with VAP was $61,092 per subject, and $25,142 for those without a VAP. No significant differences were evident in the cost of respiratory physiotherapy as a per cent of the cost of their ICU MV bed days, with findings of 1.4 per cent in those with VAP and 1.1 per cent in those without VAP. It can be concluded from these findings that VAP does have a significant influence on morbidity and costs in patients with ABI.

Chapter 8 References

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Patient Information Sheet and Consent Form

The effect of chest physiotherapy on the prevention and treatment of pneumonia for intensive care patients with head injury

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Introduction

Many patients after an acquired brain injury are admitted to the intensive care unit as part of the management. Because of their injury, and the management that is required, patients after an acquired brain injury may be at risk of developing problems with their lungs. Chest physiotherapy is often given to patients in the intensive care unit to try and prevent lung problems from occurring or to treat any chest infections or pneumonia that may occur. At Royal Perth Hospital physiotherapists are available 24-hours a day, 7 days a week to provide this treatment. However there is no evidence that patients after an acquired brain injury benefit from having chest physiotherapy in the intensive care to help their lung function. Therefore the aim of this study is to establish if in fact it is worth patients receiving chest physiotherapy for their lungs after an acquired brain injury.

What does the trial involve?

The study will involve two groups: one that receives regular chest physiotherapy during their time in intensive care and one that does not. The nursing and medical care will not be influenced by this trial. There are no additional measurements or tests involved by being in this study, and involvement in this study will not pose any known impact on the patient's potential recovery. The chest physiotherapy that patients will receive will be standard, clinically accepted treatments. The study will not introduce any new physiotherapy techniques; it only seeks to investigate clinically accepted interventions in an attempt to determine what is 'best practice". The provision of a '24 hour' service ensures that no patient will be compromised or denied any necessary physiotherapy services by inclusion in this study. Measurements that will be looked at as part of the study include how long the patient is on a breathing machine, how long they spend in intensive care, how their lungs are working and how many patients have problems with their lungs such as pneumonia.

Benefits and risks

There are no major known risks involved in this study and it has the approval of the intensive care specialists and your physiotherapist. As mentioned previously, there are no additional measurements or tests involved by being in this study and involvement in this study will not pose any known impact on the patient's potential recovery.

The majority of patients with acquired brain injury do not remember the physiotherapy treatment in the ICU. There may be some minimal discomfort during chest physiotherapy as it may involve the patient having their position in the bed changed, receiving a technique that is like taking a big breath, and involuntary coughing. Most patients with acquired brain injury have a drip giving them

Appendix 2 Part A - Summary Results of Group Comparison

Appendix 2.1 Part A – Intention to Treat Analysis

A 2.1.1 Part A intention to treat analysis: demographic and dependent variable details

Success of the randomisation process in achieving comparable groups for Part A of the study, based on intention to treat philosophy, was assessed using Chi Square tests (on nominal data) (Appendix Table 2.1.1) and t-tests for independent samples (on continuously distributed variables) (Appendix Table 2.1.2). This section also provides results of the t-tests for independent samples used to investigate differences between groups for the dependent variables.

Appendix Table 2.1.1 Pearson chi-square test results- Part A intention to treat analysis

Group randomisation by:	Value	df	p value
Gender	6.534	1	0.011
Race	2.032 [a]	2	0.362
History of presenting complaint	3.175 [b]	4	0.529
Chest injuries	0.034	1	0.853
Respiratory history	2.571 [c]	3	0.463
Smoking history	3.106 [d]	3	0.376
Chronic sputum production	0.000	1	1.000
Ventilator associated pneumonia	0.983	1	0.322
Antibiotics utilised	0.112	1	0.737
Primary bacteriology	7.045 [e]	6	0.317
Withdrawn	2.531	1	0.112
Lobar collapse	0.032	1	0.859
Bronchoscopy	2.118 [f]	1	0.146
Re-ventilation	0.546	1	0.460
Re-admission to ICU	0.000 [g]	1	1.000
Mortality	2.464	1	0.116
Deceased in ICU	0.559 [h]	1	0.455

Number of Valid Cases = 144

a 2 cells (33.3%) have expected count less than 5. The minimum expected count is 3.00.
b 4 cells (40.0%) have expected count less than 5. The minimum expected count is 4.50.
c 4 cells (50.0%) have expected count less than 5. The minimum expected count is 3.50.
d 2 cells (25.0%) have expected count less than 5. The minimum expected count is .99.
e 11 cells (78.6%) have expected count less than 5. The minimum expected count is .42
f 2 cells (50.0%) have expected count less than 5. The minimum expected count is 4.00.
g 2 cells (50.0%) have expected count less than 5. The minimum expected count is 2.00.
h 1 cells (25.0%) have expected count less than 5. The minimum expected count is 4.97.

Appendix Table 2.1.2 Independent samples t-test results - Part A intention to treat analysis

Variable		Levene's Test for Equality of Variances		t-test for Equality of Means						
		F	p value	t	df	p value	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
									Lower	Upper
age	Equal variances assumed	0.638	0.426	1.453	142	0.148	4.720	3.249	-1.701	11.145
body mass index	Equal variances assumed	0.213	0.645	2.069	124	0.041	2.193	1.059	0.095	4.290
Glasgow coma scale on admission to ICU	Equal variances assumed	0.170	0.681	1.269	142	0.206	0.420	0.328	-0.232	1.066
APACHE - worst score in first day	Equal variances assumed	0.037	0.847	-0.223	140	0.824	-0.210	0.946	-2.081	1.659
VAP diagnosis day	Equal variances assumed	2.882	0.100	0.381	31	0.706	0.470	1.234	-2.047	2.987
duration of MV (hrs)	Equal variances assumed	5.656	0.019	-1.344	142	0.181	-33.513	24.927	-82.789	15.762
	Equal variances not assumed			-1.344	125.819	0.181	-33.513	24.927	-82.843	15.817
length of ICU stay (hrs)	Equal variances assumed	8.574	0.004	-1.233	142	0.220	-32.178	26.095	-83.763	19.406
	Equal variances not assumed			-1.233	123.344	0.220	-32.178	26.095	-83.830	19.473
length of hospital stay (days)	Equal variances assumed	4.639	0.033	1.730	142	0.086	10.965	6.338	-1.565	23.495
	Equal variances not assumed			1.730	93.323	0.087	10.965	6.338	-1.622	23.551
clinical pulmonary infection score Day 1	Equal variances assumed	0.368	0.545	0.208	142	0.835	0.080	0.400	-0.708	0.875
clinical pulmonary infection score Day 2	Equal variances assumed	0.002	0.969	-1.148	141	0.253	-0.470	0.408	-1.275	0.338
clinical pulmonary infection score Day 3	Equal variances assumed	1.377	0.243	0.125	123	0.901	0.060	0.489	-0.907	1.029
clinical pulmonary infection score Day 4	Equal variances assumed	0.173	0.678	0.662	99	0.510	0.330	0.494	-0.654	1.308

Variable		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	p value	t	df	p value	Mean Difference	Std. Error Difference	Lower	Upper
clinical pulmonary infection score Day 5	Equal variances assumed	0.516	0.475	0.511	79	0.611	0.260	0.511	-0.756	1.278
clinical pulmonary infection score Day 6	Equal variances assumed	1.314	0.256	-0.912	59	0.366	-0.610	0.665	-1.938	0.725
clinical pulmonary infection score Day 7	Equal variances assumed	1.110	0.297	-0.346	55	0.731	-0.210	0.621	-1.459	1.029
clinical pulmonary infection score Day 8	Equal variances assumed	0.831	0.367	-0.676	45	0.503	-0.460	0.675	-1.816	0.903
clinical pulmonary infection score Day 9	Equal variances assumed	1.819	0.187	-0.741	31	0.464	-0.580	0.780	-2.168	1.012
clinical pulmonary infection score Day 10	Equal variances assumed	3.010	0.096	-1.707	23	0.101	-1.600	0.940	-3.548	0.339
clinical pulmonary infection score Day 11	Equal variances assumed	0.556	0.465	-0.846	19	0.408	-0.930	1.098	-3.227	1.370
clinical pulmonary infection score Day 12	Equal variances assumed	0.549	0.471	-0.152	14	0.882	-0.190	1.255	-2.883	2.502
clinical pulmonary infection score Day 13	Equal variances assumed	0.044	0.839	0.118	11	0.908	0.170	1.412	-2.941	3.274
clinical pulmonary infection score Day 14	Equal variances assumed	0.292	0.602	-1.208	9	0.258	-1.900	1.573	-5.457	1.657
clinical pulmonary infection score Day 15	Equal variances assumed	0.400	0.561	-3.500	4	0.025	-2.330	0.667	-4.184	-0.482
clinical pulmonary infection score Day 16	Equal variances assumed	15.284	0.030	0.099	3	0.927	0.330	3.361	-10.363	11.030
	Equal variances not assumed			0.080	1.184	0.948	0.330	4.177	-36.725	37.392
clinical pulmonary infection score Day 17	Equal variances assumed	.	.	-1.155	1	0.454	-4.000	3.464	-48.016	40.016

Variable		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	p value	t	df	p value	Mean Difference	Std. Error Difference	Lower	Upper
PaO_2/FiO_2 best of day 1	Equal variances assumed	0.721	0.397	-0.558	141	0.578	-12.140	21.778	-55.198	30.908
PaO_2/FiO_2 best of day 2	Equal variances assumed	1.057	0.306	-0.931	138	0.354	-16.960	18.221	-52.988	19.071
PaO_2/FiO_2 best of day 3	Equal variances assumed	0.827	0.365	-1.127	119	0.262	-21.130	18.751	-58.263	15.994
PaO_2/FiO_2 best of day 4	Equal variances assumed	1.123	0.292	-0.854	95	0.395	-17.520	20.517	-58.251	23.210
PaO_2/FiO_2 best of day 5	Equal variances assumed	2.507	0.117	-0.709	77	0.480	-13.900	19.593	-52.914	25.115
PaO_2/FiO_2 best of day 6	Equal variances assumed	0.122	0.728	0.380	57	0.705	9.320	24.542	-39.823	58.467
PaO_2/FiO_2 best of day 7	Equal variances assumed	1.726	0.195	0.261	51	0.795	6.030	23.093	-40.329	52.393
PaO_2/FiO_2 best of day 8	Equal variances assumed	3.210	0.081	-0.995	41	0.326	-25.340	25.466	-76.769	26.089
PaO_2/FiO_2 best of day 9	Equal variances assumed	13.878	0.001	-0.706	29	0.486	-21.250	30.123	-82.861	40.357
	Equal variances not assumed			-0.628	15.231	0.539	-21.250	33.817	-93.237	50.733
PaO_2/FiO_2 best of day 10	Equal variances assumed	0.085	0.773	0.835	23	0.412	34.280	41.066	-50.675	119.230
PaO_2/FiO_2 best of day 11	Equal variances assumed	2.584	0.124	-0.455	19	0.654	-19.930	43.823	-111.651	71.794
PaO_2/FiO_2 best of day 12	Equal variances assumed	10.130	0.007	-1.706	13	0.112	-74.61	43.724	-169.067	19.852
	Equal variances not assumed			-1.608	7.022	0.152	-74.61	46.399	-184.252	35.038
PaO_2/FiO_2 best of day 13	Equal variances assumed	1.753	0.215	-0.008	10	0.994	-0.670	80.004	-178.926	177.592
PaO_2/FiO_2 best of day 14	Equal variances assumed	0.212	0.659	-2.116	7	0.072	-114.330	54.043	-242.125	13.459
PaO_2/FiO_2 best of day 15	Equal variances assumed	.	.	-0.401	2	0.727	-21.670	53.967	-253.868	210.535
PaO_2/FiO_2 best of day 16	Equal variances assumed	.	.	3.918	2	0.059	154.500	39.437	-15.182	324.182
PaO_2/FiO_2 best of day 17	Equal variances assumed	.	.	8.259	1	0.077	164.500	19.919	-88.590	417.590
PaO_2/FiO_2 best of day 18	Equal variances assumed	.	.	.	0	.	99.000	.	.	.

Variable		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	p value	t	df	p value	Mean Difference	Std. Error Difference	Lower	Upper
PaO_2/FiO_2 worst of day 1	Equal variances assumed	0.000	0.984	-0.546	141	0.586	-9.820	17.992	-45.394	25.745
PaO_2/FiO_2 worst of day 2	Equal variances assumed	5.833	0.017	-0.578	138	0.564	-9.220	15.949	-40.755	22.317
	Equal variances not assumed			-0.580	130.162	0.563	-9.220	15.887	-40.648	22.210
PaO_2/FiO_2 worst of day 3	Equal variances assumed	4.701	0.032	-1.110	119	0.269	-19.840	17.874	-55.229	15.556
	Equal variances not assumed			-1.107	106.653	0.271	-19.840	17.922	-55.367	15.694
PaO_2/FiO_2 worst of day 4	Equal variances assumed	3.703	0.057	-0.707	95	0.481	-14.160	20.038	-53.943	25.620
PaO_2/FiO_2 worst of day 5	Equal variances assumed	4.755	0.032	-1.378	77	0.172	-26.760	19.412	-65.409	11.898
	Equal variances not assumed			-1.328	59.688	0.189	-26.760	20.141	-67.047	13.537
PaO_2/FiO_2 worst of day 6	Equal variances assumed	17.746	0.000	-1.640	57	0.106	-33.860	20.642	-75.195	7.477
	Equal variances not assumed			-1.517	33.475	0.139	-33.860	22.319	-79.244	11.525
PaO_2/FiO_2 worst of day 7	Equal variances assumed	2.597	0.113	-1.140	51	0.260	-22.950	20.124	-63.347	17.454
PaO_2/FiO_2 worst of day 8	Equal variances assumed	2.699	0.108	-0.936	41	0.355	-23.520	25.130	-74.267	27.236
PaO_2/FiO_2 worst of day 9	Equal variances assumed	5.522	0.026	0.292	29	0.772	7.470	25.596	-44.876	59.824
	Equal variances not assumed			0.273	19.253	0.788	7.470	27.376	-49.773	64.722

Variable		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	p value	t	df	p value	Mean Difference	Std. Error Difference	Lower	Upper
PaO_2/FiO_2 worst of day 10	Equal variances assumed	4.298	.050	0.392	23	0.699	10.780	27.489	-46.087	67.643
	Equal variances not assumed			0.339	11.143	0.741	10.780	31.795	-59.094	80.650
PaO_2/FiO_2 worst of day 11	Equal variances assumed	0.893	0.357	0.371	19	0.715	14.790	39.850	-68.621	98.192
PaO_2/FiO_2 worst of day 12	Equal variances assumed	8.382	0.013	-1.633	13	0.127	-64.320	39.398	-149.435	20.793
	Equal variances not assumed			-1.548	7.559	0.162	-64.320	41.559	-161.139	32.496
PaO_2/FiO_2 worst of day 13	Equal variances assumed	0.010	0.923	0.501	10	0.627	26.330	52.525	-90.699	143.366
PaO_2/FiO_2 worst of day 14	Equal variances assumed	0.719	0.425	-1.158	7	0.285	-87.830	75.838	-267.162	91.495
PaO_2/FiO_2 worst of day 15	Equal variances assumed	.	.	5.687	2	0.030	141.670	24.909	34.493	248.840
PaO_2/FiO_2 worst of day 16	Equal variances assumed	.	.	0.811	2	0.502	49.000	60.407	-210.910	308.910
PaO_2/FiO_2 worst of day 17	Equal variances assumed	.	.	4.940	1	0.127	77.000	15.588	-121.070	275.070
PaO_2/FiO_2 worst of day 18	Equal variances assumed	.	.	.	0		-28.000	.	.	.

Appendix 2.2 Part A – Subjects Not Receiving All Allocated Interventions vs. All Others

A 2.2.1 Part A subjects not receiving all allocated interventions vs. all others - demographic and dependent variable details

Sixteen Part A subjects did not receive all their allocated interventions (Section 4.1.6). Chi Square (Appendix Table 2.2.1) and t-tests (Appendix Table 2.2.2) were undertaken to compare these 16 Part A subjects not receiving all their allocated respiratory physiotherapy interventions to all those who did complete their intervention. This was undertaken in an attempt to identify any demographic or outcome factors that may have been different in those not receiving their allocated intervention, results of which are summarised in this section.

Appendix Table 2.2.3 Part A subjects not receiving all allocated interventions vs. all others

Receiving all allocated intervention by:	Value	df	p value
Gender	0.131	1	0.718
Race	0.643 [a]	2	0.725
History of presenting complaint	7.373 [b]	4	0.117
Chest injuries	0.835 [c]	1	0.361
Respiratory history	3.260 [d]	3	0.353
Smoking history	0.914 [e]	3	0.822
Chronic sputum production	0.013 [f]	1	0.908
Ventilator associated pneumonia	0.177 [g]	1	0.674
Antibiotics utilised	0.352	1	0.553
Lobar collapse	0.193	1	0.660
Bronchoscopy	1.059 [h]	1	0.303
Re-ventilation	0.758 [i]	1	0.384
Re-admission to ICU	0.514 [j]	1	0.473
Mortality	20.334 [k]	1	0.000
Deceased in ICU	0.359 [l]	1	0.549

Number of Valid Cases = 144

a 2 cells (33.3%) have expected count less than 5. The minimum expected count is .67
b 3 cells (30.0%) have expected count less than 5. The minimum expected count is 1.00
c 1 cells (25.0%) have expected count less than 5. The minimum expected count is 4.56
d 3 cells (37.5%) have expected count less than 5. The minimum expected count is .78
e 3 cells (37.5%) have expected count less than 5. The minimum expected count is .22
f 1 cells (25.0%) have expected count less than 5. The minimum expected count is 1.11
g 1 cells (25.0%) have expected count less than 5. The minimum expected count is 3.67
h 1 cells (25.0%) have expected count less than 5. The minimum expected count is .89
I 1 cells (25.0%) have expected count less than 5. The minimum expected count is 2.11
j 2 cells (50.0%) have expected count less than 5. The minimum expected count is .44
k 1 cells (25.0%) have expected count less than 5. The minimum expected count is 3.78
l 1 cells (25.0%) have expected count less than 5. The minimum expected count is 4.21

Appendix Table 2.2.4 Independent samples t-test results - Part A subjects not receiving all allocated interventions vs. all others

Variable		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	p value	t	df	p value	Mean Difference	Std. Error Difference	Lower	Upper
age	Equal variances assumed	0.437	0.510	2.328	142	0.021	11.900	5.111	1.794	22.002
body mass index	Equal variances assumed	1.023	0.314	0.820	124	0.414	1.630	1.989	-2.306	5.567
Glasgow coma scale on admission to ICU	Equal variances assumed	1.575	0.212	-2.068	142	0.040	-1.070	0.518	-2.093	-0.047
APACHE - worst score in first day	Equal variances assumed	1.372	0.243	2.939	141	0.004	4.260	1.449	1.394	7.124
duration of MV (hrs)	Equal variances assumed	1.594	0.209	-1.275	142	0.204	-50.588	39.684	-129.035	27.860
length of ICU stay (hrs)	Equal variances assumed	0.152	0.697	-1.739	142	0.084	-71.817	41.301	-153.462	9.828
length of hospital stay (days)	Equal variances assumed	1.290	0.258	-1.848	142	0.067	-18.606	10.070	-38.512	1.300

Appendix 2.3 Part A – Analysis by Treatment

A 2.3.1 Part A – Analysis by treatment - demographic and dependent variable details

Data were analysed both using an intention to treat philosophy and analysis by treatment principle. Results of the 'analysis by treatment' for Part A demographic and dependent variables are summarised in this section.

Appendix Table 2.3.1 Pearson chi-square test results - Part A analysis by treatment

Group randomisation by:	Value	df	p value
Gender	6.767	1	0.009
Race	3.535 [a]	2	0.171
History of presenting complaint	2.719 [b]	4	0.606
Chest injuries	0.119	1	0.730
Respiratory history	2.144 [c]	3	0.543
Smoking history	2.694 [d]	3	0.441
Chronic sputum production	0.040 [e]	1	0.841
Ventilator associated pneumonia	1.275	1	0.259
Antibiotics utilised	0.016	1	0.898
Lobar collapse	0.042	1	0.838
Bronchoscopy	2.558 [f]	1	0.110
Re-ventilation	0.524	1	0.469
Re-admission to ICU	0.009 [g]	1	0.924
Mortality	0.883	1	0.347
Deceased in ICU	1.806 [h]	1	0.179

Number of Valid Cases = 128

a 3 cells (50.0%) have expected count less than 5. The minimum expected count is 2.38
b 4 cells (40.0%) have expected count less than 5. The minimum expected count is 3.34
c 4 cells (50.0%) have expected count less than 5. The minimum expected count is 2.38
d 3 cells (37.5%) have expected count less than 5. The minimum expected count is .94
e 2 cells (50.0%) have expected count less than 5. The minimum expected count is 4.29
f 2 cells (50.0%) have expected count less than 5. The minimum expected count is 3.81
g 2 cells (50.0%) have expected count less than 5. The minimum expected count is 1.91
h 2 cells (50.0%) have expected count less than 5. The minimum expected count is 3.48

Appendix Table 2.3.2 Independent samples t-test results - Part A analysis by treatment

Variable		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	p value	t	df	p value	Mean Difference	Std. Error Difference	Lower	Upper
age	Equal variances assumed	0.312	0.577	1.484	126	0.140	4.950	3.336	-1.653	11.550
body mass index	Equal variances assumed	0.011	0.917	2.515	114	0.013	2.571	1.022	0.546	4.596
Glasgow coma scale on admission to ICU	Equal variances assumed	0.006	0.937	.968	126	0.335	0.340	0.347	-0.351	1.023
APACHE - worst score in first day	Equal variances assumed	0.018	0.893	-.306	125	0.760	-0.290	0.946	-2.161	1.583
VAP diagnosis day	Equal variances assumed	1.490	0.232	0.655	28	0.518	0.860	1.312	-1.828	3.548
duration of MV (hrs)	Equal variances assumed	6.205	0.014	-1.301	126	0.196	-35.175	27.032	-88.671	18.321
	Equal variances not assumed			-1.278	103.259	0.204	-35.1745	27.524	-89.761	19.411
length of ICU stay (hrs)	Equal variances assumed	9.022	0.003	-1.268	126	0.207	-35.420	27.934	-90.702	19.861
	Equal variances not assumed			-1.243	99.655	0.217	-35.420	28.506	-91.977	21.137
length of hospital stay (days)	Equal variances assumed	3.801	0.053	1.375	126	0.171	9.648	7.0145	-4.235	23.530

Appendix 3 Part B - Summary Results of Group Comparison

Appendix 3.1 Part B –Intention to Treat Analysis

A 3.1.1 Part B –Intention to treat analysis: demographic and dependent variable details

Success of the randomisation process in achieving comparable groups for Part B of the study, based on intention to treat philosophy, was assessed using Chi Square tests (on nominal data) (Appendix Table 3.1.1) and t-tests for independent samples (on continuously distributed variables) (Appendix Table 3.1.2). This section also provides results of the t-tests for independent samples used to investigate differences between groups for the dependent variables.

Appendix Table 3.1.1 Pearson chi-square test results - Part B intention to treat analysis

Group randomisation by:	Value	df	p value
Gender	0.732	1	0.392
Race	2.262 [a]	1	0.133
History of presenting complaint	2.201 [b]	4	0.699
Chest injuries	0.022	1	0.881
Respiratory history	1.686 [c]	3	0.640
Smoking history	3.708 [d]	3	0.295
Chronic sputum production	0.437 [e]	1	0.509
Withdrawn	0.004 [f]	1	0.948
Antibiotics utilised	0.002 [g]	1	0.965
Lobar collapse	4.251 [h]	1	0.039
Bronchoscopy	4.370 [i]	1	0.509
Re-ventilation	0.030 [j]	1	0.582
Mortality	0.004 [k]	1	0.948
Deceased in ICU	0.004 [l]	1	0.948

Number of Valid Cases = 33

a 2 cells (50.0%) have expected count less than 5. The minimum expected count is .97
b 8 cells (80.0%) have expected count less than 5. The minimum expected count is .48
c 6 cells (75.0%) have expected count less than 5. The minimum expected count is .97
d 4 cells (50.0%) have expected count less than 5. The minimum expected count is .47
e 2 cells (50.0%) have expected count less than 5. The minimum expected count is 1.45
f 2 cells (50.0%) have expected count less than 5. The minimum expected count is 1.94
g 2 cells (50.0%) have expected count less than 5. The minimum expected count is .97
h 2 cells (50.0%) have expected count less than 5. The minimum expected count is 4.36
I 2 cells (50.0%) have expected count less than 5. The minimum expected count is 1.45
j 2 cells (50.0%) have expected count less than 5. The minimum expected count is 1.45
k 2 cells (50.0%) have expected count less than 5. The minimum expected count is 1.94
l 2 cells (50.0%) have expected count less than 5. The minimum expected count is 1.94

Appendix Table 3.1.2 Independent samples t-test results - Part B intention to treat analysis

Variable		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	p value	t	df	p value	Mean Difference	Std. Error Difference	Lower	Upper
age	Equal variances assumed	0.637	0.431	-0.644	31	0.525	-3.820	5.935	-15.925	8.285
body mass index	Equal variances assumed	0.144	0.707	-0.237	31	0.814	-0.562	2.374	-5.402	4.279
Glasgow coma scale on admission to ICU	Equal variances assumed	0.000	0.985	-0.603	31	0.551	-0.410	0.677	-1.789	0.973
APACHE - worst score in first day	Equal variances assumed	0.003	0.960	1.250	31	0.221	2.750	2.200	-1.737	7.237
duration of MV (hrs)	Equal variances assumed	0.040	0.843	-0.143	31	0.887	-8.969	62.784	-137.018	119.080
length of ICU stay (hrs)	Equal variances assumed	0.000	0.990	-0.205	31	0.839	-13.219	64.446	-144.658	118.2218
length of hospital stay (days)	Equal variances assumed	3.400	0.075	1.230	31	0.228	14.180	11.526	-9.327	37.687
clinical pulmonary infection score Day 1	Equal variances assumed	0.006	0.940	0.150	31	0.882	0.060	0.369	-0.696	0.807
clinical pulmonary infection score Day 2	Equal variances assumed	1.477	0.233	0.093	31	0.926	0.070	0.790	-1.538	1.685
clinical pulmonary infection score Day 3	Equal variances assumed	2.030	0.165	0.914	29	0.368	0.670	0.729	-0.824	2.158
clinical pulmonary infection score Day 4	Equal variances assumed	0.821	0.372	0.675	29	0.505	0.640	0.945	-1.294	2.569
clinical pulmonary infection score Day 5	Equal variances assumed	1.058	0.314	-0.633	25	0.533	-0.580	0.922	-2.482	1.315
clinical pulmonary infection score Day 6	Equal variances assumed	2.424	0.133	-0.346	23	0.732	-0.350	1.013	-2.446	1.745

NB day number represents day post-diagnosis of VAP and transfer to Part B of the study

Variable		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	p value	t	df	p value	Mean Difference	Std. Error Difference	Lower	Upper
clinical pulmonary infection score Day 7	Equal variances assumed	0.214	0.648	0.277	22	0.785	0.290	1.033	-1.856	2.427
clinical pulmonary infection score Day 8	Equal variances assumed	0.472	0.500	-0.106	19	0.917	-0.130	1.205	-2.650	2.395
clinical pulmonary infection score Day 9	Equal variances assumed	2.350	0.149	-0.154	13	0.880	-0.210	1.387	-3.212	2.783
clinical pulmonary infection score Day 10	Equal variances assumed	1.724	0.214	0.329	12	0.748	0.630	1.899	-3.513	4.763
clinical pulmonary infection score Day 11	Equal variances assumed	2.194	0.189	-1.177	6	0.284	-1.500	1.275	-4.619	1.619
clinical pulmonary infection score Day 12	Equal variances assumed	0.235	0.653	-1.809	4	0.145	-2.000	1.106	-5.069	1.069
clinical pulmonary infection score Day 13	Equal variances assumed	0.727	0.442	-2.214	4	0.091	-2.330	1.054	-5.260	0.593
clinical pulmonary infection score Day 14	Equal variances assumed	3.200	0.148	-3.578	4	0.023	-2.670	0.745	-4.736	-0.597
clinical pulmonary infection score Day 15	Equal variances assumed	.	.	-0.472	2	0.683	-1.670	3.528	-16.845	13.512
clinical pulmonary infection score Day 16	Equal variances assumed	.	.	-4.041	1	0.154	-3.500	0.866	-14.504	7.504

NB day number represents day post-diagnosis of VAP and transfer to Part B of the study

Variable		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	p value	t	df	p value	Mean Difference	Std. Error Difference	Lower	Upper
PaO_2/FiO_2 best of day 1	Equal variances assumed	0.155	0.697	-2.080	31	0.046	-76.740	36.887	-151.971	-1.507
PaO_2/FiO_2 best of day 2	Equal variances assumed	2.064	0.161	-1.051	31	0.301	-32.190	30.634	-94.673	30.284
PaO_2/FiO_2 best of day 3	Equal variances assumed	0.016	0.900	-0.824	29	0.417	-32.020	38.857	-111.491	47.450
PaO_2/FiO_2 best of day 4	Equal variances assumed	2.624	0.116	-1.701	28	0.100	-55.270	32.484	-121.806	11.273
PaO_2/FiO_2 best of day 5	Equal variances assumed	2.279	0.144	0.458	25	0.651	16.320	35.621	-57.046	89.679
PaO_2/FiO_2 best of day 6	Equal variances assumed	0.035	0.853	-0.995	23	0.330	-35.060	35.250	-107.979	37.862
PaO_2/FiO_2 best of day 7	Equal variances assumed	0.071	0.793	-0.634	22	0.532	-26.000	40.982	-110.992	58.992
PaO_2/FiO_2 best of day 8	Equal variances assumed	0.697	0.416	-0.772	16	0.451	-33.270	43.084	-124.608	58.058
PaO_2/FiO_2 best of day 9	Equal variances assumed	0.008	0.930	-0.727	16	0.478	-25.000	34.409	-97.944	47.944
PaO_2/FiO_2 best of day 10	Equal variances assumed	0.422	0.531	-1.254	10	0.239	-71.600	57.119	-198.869	55.669
PaO_2/FiO_2 best of day 11	Equal variances assumed	0.045	0.840	0.325	5	0.758	25.250	77.699	-174.481	224.981
PaO_2/FiO_2 best of day 12	Equal variances assumed	0.440	0.543	-0.311	4	0.771	-40.330	129.670	-400.354	319.687
PaO2/FiO2 best of day 13	Equal variances assumed	0.149	0.719	0.405	4	0.706	25.670	63.352	-150.226	201.559

NB day number represents day post-diagnosis of VAP and transfer to Part B of the study

Variable		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	p value	t	df	p value	Mean Difference	Std. Error Difference	Lower	Upper
PaO2/FiO2 best of day 14	Equal variances assumed	2.190	0.213	1.122	4	0.325	64.670	57.626	-95.329	224.663
PaO2/FiO2 best of day 15	Equal variances assumed	.	.	0.341	2	0.765	35.000	102.574	-406.338	476.338
PaO2/FiO2 best of day 16	Equal variances assumed	.	.	0.178	1	0.888	20.000	112.583	-1410.506	1450.506
PaO_2/FiO_2 worst of day 1	Equal variances assumed	1.019	0.321	-1.131	31	0.267	-21.180	18.733	-59.387	17.026
PaO_2/FiO_2 worst of day 2	Equal variances assumed	0.086	0.772	-1.234	31	0.227	-28.510	23.103	-75.626	18.611
PaO_2/FiO_2 worst of day 3	Equal variances assumed	1.553	0.223	-1.331	29	0.194	-38.880	29.212	-98.624	20.866
PaO_2/FiO_2 worst of day 4	Equal variances assumed	0.776	0.386	-1.268	28	0.215	-43.930	34.644	-114.899	27.032
PaO_2/FiO_2 worst of day 5	Equal variances assumed	9.470	0.005	0.296	25	0.769	10.930	36.888	-65.039	86.905
	Equal variances not assumed			0.276	15.123	0.786	10.930	39.632	-73.480	95.347
PaO_2/FiO_2 worst of day 6	Equal variances assumed	0.348	0.561	-0.537	23	0.596	-19.030	35.405	-92.267	54.215
PaO_2/FiO_2 worst of day 7	Equal variances assumed	0.264	0.612	-0.783	22	0.442	-30.200	38.564	-110.177	49.777
PaO_2/FiO_2 worst of day 8	Equal variances assumed	1.820	0.204	-2.198	11	0.050	-118.070	53.716	-236.299	0.156

NB day number represents day post-diagnosis of VAP and transfer to Part B of the study

Variable		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	p value	t	df	p value	Mean Difference	Std. Error Difference	Lower	Upper
PaO_2/FiO_2 worst of day 9	Equal variances assumed	2.437	0.147	-0.656	11	0.526	-32.500	49.579	-141.622	76.622
PaO_2/FiO_2 worst of day 10	Equal variances assumed	6.502	0.029	-0.628	10	0.544	-37.000	58.915	-168.270	94.270
	Equal variances not assumed			-0.552	5.055	0.604	-37.000	67.018	-208.712	134.712
PaO_2/FiO_2 worst of day 11	Equal variances assumed	1.765	0.241	0.058	5	0.956	4.580	79.572	-199.962	209.129
PaO_2/FiO_2 worst of day 12	Equal variances assumed	0.264	0.635	0.384	4	0.721	30.330	79.004	-189.016	249.682
	Equal variances not assumed	0.234	0.654	-0.321	4	0.764	-14.330	44.685	-138.400	109.733
PaO_2/FiO_2 worst of day 13	Equal variances assumed	1.335	0.312	0.892	4	0.423	74.670	83.746	-157.850	307.184
PaO_2/FiO_2 worst of day 14	Equal variances assumed	.	.	0.249	2	0.827	23.000	92.463	-374.834	420.834
PaO_2/FiO_2 worst of day 15	Equal variances assumed	.	.	-0.452	1	0.730	-54.000	119.512	-1572.538	1464.538

NB day number represents day post-diagnosis of VAP and transfer to Part B of the study

Appendix 3.2 Part B – Subjects Not Receiving All Allocated Interventions vs. All Others

A 3.2.1 Part B subjects not receiving all allocated interventions vs. all others - demographic and dependent variable details

Four Part B subjects did not receive all their allocated interventions (Section 4.2.4). Chi Square (Appendix Table 3.2.1) and t-tests (Appendix Table 3.2.2) were undertaken to compare these four Part B subjects not receiving all their allocated respiratory physiotherapy interventions to all those who did complete their intervention. This was undertaken in an attempt to identify any demographic or outcome factors that may have been different in those not receiving their allocated intervention, results of which are summarised in this section.

Appendix Table 3.2.1 Part B subjects not receiving all allocated interventions vs. all others

Receiving all allocated interventions by:	Value	df	p value
Gender	2.936 [a]	1	0.087
Race	0.294 [b]	1	0.588
History of presenting complaint	10.082 [c]	4	0.039
Chest injuries	0.107 [d]	1	0.744
Respiratory history	1.036 [e]	3	0.792
Smoking history	10.482 [f]	3	0.015
Chronic sputum production	0.455 [g]	1	0.500
Antibiotics utilised	0.294 [h]	1	0.588
Lobar collapse	1.185 [i]	1	0.276
Bronchoscopy	1.394 [j]	1	0.238
Re-ventilation	0.455 [k]	1	0.500
Mortality	0.628 [l]	1	0.428
Deceased in ICU	0.628 [m]	1	0.428

Number of Valid Cases = 33

a 2 cells (50.0%) have expected count less than 5. The minimum expected count is 1.45
b 3 cells (75.0%) have expected count less than 5. The minimum expected count is .24
c 8 cells (80.0%) have expected count less than 5. The minimum expected count is .12.
d 2 cells (50.0%) have expected count less than 5. The minimum expected count is 1.70
e 6 cells (75.0%) have expected count less than 5. The minimum expected count is .24
f 6 cells (75.0%) have expected count less than 5. The minimum expected count is .13
g 3 cells (75.0%) have expected count less than 5. The minimum expected count is .36
h 3 cells (75.0%) have expected count less than 5. The minimum expected count is .24
i 2 cells (50.0%) have expected count less than 5. The minimum expected count is 1.09
j 3 cells (75.0%) have expected count less than 5. The minimum expected count is .36
k 3 cells (75.0%) have expected count less than 5. The minimum expected count is .36
l 3 cells (75.0%) have expected count less than 5. The minimum expected count is .48
m 3 cells (75.0%) have expected count less than 5. The minimum expected count is .48

Appendix Table 3.2.2 Independent samples t-test results - Part B subjects not receiving all allocated interventions vs. all others

Variable		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	p value	t	df	p value	Mean Difference	Std. Error Difference	Lower	Upper
age	Equal variances assumed	0.067	0.798	1.659	31	0.107	14.540	8.768	-3.340	32.426
body mass index	Equal variances assumed	0.013	0.911	-0.303	31	0.764	-1.040	3.448	-8.075	5.989
Glasgow coma scale on admission to ICU	Equal variances assumed	0.751	0.393	2.404	31	0.022	2.300	0.958	0.349	4.255
APACHE - worst score in first day	Equal variances assumed	0.242	0.626	-0.209	31	0.836	-.7590	3.635	-8.173	6.655
duration of MV (hrs)	Equal variances assumed	1.459	0.236	0.840	31	0.407	79.873	95.096	-114.076	273.823
length of ICU stay (hrs)	Equal variances assumed	2.578	0.118	1.668	31	0.105	157.780	94.600	-35.157	350.717
length of hospital stay (days)	Equal variances assumed	0.071	0.792	0.833	31	0.411	14.885	17.876	-21.573	51.344

Appendix 3.3 Part B – Analysis by treatment

A 3.3.1 Part B analysis by treatment: demographic and dependent variable details

Data from Part B were analysed both using an intention to treat philosophy and analysis by treatment principle. Results of the 'analysis by treatment' for Part B demographic and dependent variables are summarised in this section.

Appendix Table 3.3.1 Pearson chi-square test results - Part B analysis by treatment

Group randomisation by:	Value	df	p value
Gender	0.277 [a]	1	0.599
Race	2.302 [b]	1	0.129
History of presenting complaint	1.083 [c]	3	0.781
Chest injuries	0.024	1	0.876
Respiratory history	1.389 [d]	3	0.708
Smoking history	1.323 [e]	2	0.516
Chronic sputum production	0.453 [f]	1	0.501
Antibiotics utilised	0.003 [g]	1	0.960
Lobar collapse	5.179 [h]	1	0.023
Bronchoscopy	0.003 [i]	1	0.960
Re-ventilation	0.299 [j]	1	0.584
Mortality	0.006 [k]	1	0.941
Deceased in ICU	0.006 [l]	1	0.941

Number of Valid Cases = 29

a 2 cells (50.0%) have expected count less than 5. The minimum expected count is 4.34
b 2 cells (50.0%) have expected count less than 5. The minimum expected count is .97
c 6 cells (75.0%) have expected count less than 5. The minimum expected count is .97
d 6 cells (75.0%) have expected count less than 5. The minimum expected count is .97
e 3 cells (50.0%) have expected count less than 5. The minimum expected count is .46
f 2 cells (50.0%) have expected count less than 5. The minimum expected count is 1.45
g 2 cells (50.0%) have expected count less than 5. The minimum expected count is .97
h 2 cells (50.0%) have expected count less than 5. The minimum expected count is 3.38
i 2 cells (50.0%) have expected count less than 5. The minimum expected count is .97
j 2 cells (50.0%) have expected count less than 5. The minimum expected count is 1.45
k 2 cells (50.0%) have expected count less than 5. The minimum expected count is 1.93
l 2 cells (50.0%) have expected count less than 5. The minimum expected count is 1.93

Appendix Table 3.3.2 Independent samples t-test results - Part B analysis by treatment

Variable		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	p value	t	df	p value	Mean Difference	Std. Error Difference	Lower	Upper
age	Equal variances assumed	2.557	0.121	-0.713	27	0.482	-4.300	6.027	-16.661	8.070
body mass index	Equal variances assumed	0.693	0.412	-0.608	27	0.548	-1.522	2.502	-6.655	3.612
Glasgow coma scale on admission to ICU	Equal variances assumed	0.910	0.349	-1.263	27	0.218	-0.790	0.626	-2.075	0.494
APACHE - worst score in first day	Equal variances assumed	0.009	0.927	1.924	27	0.065	4.430	2.305	-0.295	9.162
duration of MV (hrs)	Equal variances assumed	0.484	0.492	0.038	27	0.970	2.427	64.323	-129.554	134.408
length of ICU stay (hrs)	Equal variances assumed	0.484	0.493	0.148	27	0.883	9.117	61.597	-117.270	135.504
length of hospital stay (days)	Equal variances assumed	3.335	0.079	1.339	27	0.192	16.821	12.558	-8.947	42.589
clinical pulmonary infection score Day 1	Equal variances assumed	0.096	0.759	0.342	27	0.735	0.140	0.404	-0.690	0.966
clinical pulmonary infection score Day 2	Equal variances assumed	1.820	0.189	0.101	27	0.920	0.090	0.894	-1.743	1.924
clinical pulmonary infection score Day 3	Equal variances assumed	0.807	0.377	1.293	25	0.208	1.010	0.777	-.0596	2.607
clinical pulmonary infection score Day 4	Equal variances assumed	0.017	0.896	1.007	25	0.323	0.980	0.976	-1.027	2.994
clinical pulmonary infection score Day 5	Equal variances assumed	0.573	0.458	-0.261	21	0.796	-0.260	1.001	-2.342	1.819
clinical pulmonary infection score Day 6	Equal variances assumed	1.189	0.288	0.047	20	0.963	0.050	1.066	-2.173	2.273

NB day number represents day post-diagnosis of VAP and transfer to Part B of the study

Variable		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	p value.	t	df	p value	Mean Difference	Std. Error Difference	Lower	Upper
clinical pulmonary infection score Day 7	Equal variances assumed	0.151	0.702	-0.073	19	0.943	-0.080	1.149	-2.487	2.321
clinical pulmonary infection score Day 8	Equal variances assumed	0.363	0.555	-0.236	16	0.816	-0.330	1.410	-3.322	2.655
clinical pulmonary infection score Day 9	Equal variances assumed	2.075	0.175	-0.338	12	0.741	-0.500	1.479	-3.723	2.723
clinical pulmonary infection score Day 10	Equal variances assumed	0.996	0.340	-0.038	11	0.971	-0.080	1.987	-4.449	4.299
clinical pulmonary infection score Day 11	Equal variances assumed	2.194	0.189	-1.177	6	0.284	-1.500	1.275	-4.619	1.619
clinical pulmonary infection score Day 12	Equal variances assumed	0.235	0.653	-1.809	4	0.145	-2.000	1.106	-5.069	1.069
clinical pulmonary infection score Day 13	Equal variances assumed	0.727	0.442	-2.214	4	0.091	-2.330	1.054	-5.260	0.593
clinical pulmonary infection score Day 14	Equal variances assumed	3.200	0.148	-3.578	4	0.023	-2.670	0.745	-4.736	-0.597
clinical pulmonary infection score Day 15	Equal variances assumed	.	.	-0.472	2	0.683	-1.670	3.528	-16.845	13.512
clinical pulmonary infection score Day 16	Equal variances assumed	.	.	-4.041	1	0.154	-3.500	0.866	-14.504	7.504

NB day number represents day post-diagnosis of VAP and transfer to Part B of the study

Variable		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	p value	t	df	p value	Mean Difference	Std. Error Difference	Lower	Upper
PaO_2/FiO_2 best of day 1	Equal variances assumed	0.213	0.648	-1.559	27	0.131	-62.710	40.218	-145.234	19.806
PaO_2/FiO_2 best of day 2	Equal variances assumed	0.474	0.497	-1.378	27	0.180	-45.140	32.758	-112.352	22.076
PaO_2/FiO_2 best of day 3	Equal variances assumed	0.087	0.770	-1.927	25	0.065	-65.380	33.929	-135.262	4.492
PaO_2/FiO_2 best of day 4	Equal variances assumed	0.373	0.547	-2.138	24	0.043	-69.310	32.423	-136.226	-2.390
PaO_2/FiO_2 best of day 5	Equal variances assumed	2.305	0.144	0.173	21	0.864	6.300	36.455	-69.513	82.113
PaO_2/FiO_2 best of day 6	Equal variances assumed	0.112	0.741	-0.693	20	0.496	-25.780	37.179	-103.337	51.770
PaO_2/FiO_2 best of day 7	Equal variances assumed	0.287	0.598	0.000	19	1.000	0.000	41.030	-85.876	85.876
PaO_2/FiO_2 best of day 8	Equal variances assumed	1.020	0.331	-0.755	13	0.464	-36.950	48.914	-142.618	68.725
PaO_2/FiO_2 best of day 9	Equal variances assumed	0.382	0.547	-0.264	13	0.796	-9.110	34.552	-83.753	65.539
PaO_2/FiO_2 best of day 10	Equal variances assumed	0.297	0.599	-0.615	9	0.554	-32.750	53.255	-153.222	87.722
PaO_2/FiO_2 best of day 11	Equal variances assumed	0.045	0.840	0.325	5	0.758	25.250	77.699	-174.481	224.981
PaO_2/FiO_2 best of day 12	Equal variances assumed	0.440	0.543	-0.311	4	0.771	-40.330	129.670	-400.354	319.687
PaO_2/FiO_2 best of day 13	Equal variances assumed	0.149	0.719	0.405	4	0.706	25.670	63.352	-150.226	201.559
PaO_2/FiO_2 best of day 14	Equal variances assumed	2.190	0.213	1.122	4	0.325	64.670	57.626	-95.329	224.663
PaO_2/FiO_2 best of day 15	Equal variances assumed	.	.	0.341	2	0.765	35.000	102.574	-406.338	476.338
PaO_2/FiO_2 best of day 16	Equal variances assumed	.	.	0.178	1	0.888	20.000	112.583	-1410.506	1450.506

NB day number represents day post-diagnosis of VAP and transfer to Part B of the study

Variable		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	p value	t	df	p value	Mean Difference	Std. Error Difference	Lower	Upper
PaO_2/FiO_2 worst of day 1	Equal variances assumed	0.732	0.400	-0.940	27	0.355	-19.680	20.926	-62.612	23.260
PaO_2/FiO_2 worst of day 2	Equal variances assumed	0.049	0.827	-1.055	27	0.301	-24.480	23.214	-72.111	23.150
PaO_2/FiO_2 worst of day 3	Equal variances assumed	0.610	0.442	-1.661	25	0.109	-51.230	30.842	-114.752	12.290
PaO_2/FiO_2 worst of day 4	Equal variances assumed	0.282	0.600	-1.582	24	0.127	-59.000	37.286	-135.955	17.955
PaO_2/FiO_2 worst of day 5	Equal variances assumed	8.084	0.010	-0.012	21	0.991	-0.470	40.503	-84.700	83.761
	Equal variances not assumed			-0.011	12.114	0.992	-0.470	44.184	-96.639	95.700
PaO_2/FiO_2 worst of day 6	Equal variances assumed	0.547	0.468	-0.255	20	0.801	-9.770	38.233	-89.519	69.986
PaO_2/FiO_2 worst of day 7	Equal variances assumed	0.006	0.940	-0.413	19	0.684	-17.110	41.454	-103.876	69.653
PaO_2/FiO_2 worst of day 8	Equal variances assumed	0.002	0.970	-1.732	10	0.114	-86.970	50.208	-198.842	24.899
PaO_2/FiO_2 worst of day 9	Equal variances assumed	0.873	0.372	0.133	10	0.897	5.200	39.155	-82.044	92.444
PaO_2/FiO_2 worst of day 10	Equal variances assumed	6.875	0.028	0.103	9	0.920	5.500	53.312	-115.100	126.100
	Equal variances not assumed			0.086	3.883	0.936	5.500	64.261	-175.048	186.048
PaO_2/FiO_2 worst of day 11	Equal variances assumed	1.765	0.241	0.058	5	0.956	4.580	79.572	-199.962	209.129
PaO_2/FiO_2 worst of day 12	Equal variances assumed	0.264	0.635	0.384	4	0.721	30.330	79.004	-189.016	249.682
PaO_2/FiO_2 worst of day 13	Equal variances assumed	0.234	0.654	-0.321	4	0.764	-14.330	44.685	-138.400	109.733
PaO_2/FiO_2 worst of day 14	Equal variances assumed	1.335	0.312	0.892	4	0.423	74.670	83.746	-157.850	307.184
PaO_2/FiO_2 worst of day 15	Equal variances assumed	.	.	0.249	2	0.827	23.000	92.463	-374.834	420.834
PaO_2/FiO_2 worst of day 16	Equal variances assumed	.	.	-0.452	1	0.730	-54.000	119.512	-1572.538	1464.538

NB day number represents day post-diagnosis of VAP and transfer to Part B of the study

Appendix 4 Comparison of Subjects With and Without Ventilator-Associated Pneumonia

Appendix 4.1 Subjects With and Without VAP: intention to treat analysis

A 4.1.1 Comparison of subjects with and without VAP - intention to treat analysis: summary demographic and dependent variables data

Thirty-three Part A subjects satisfied criteria for diagnosis of VAP and transfer to Part B (Section 4.2). Comparison between these 33 subjects with VAP and the 111 subjects without VAP was undertaken (Section 4.3), results of which are given in this appendix. Chi Square (Appendix Table 4.1.1) and t-tests (Appendix Table 4.1.2) were undertaken to compare the subjects with VAP to those without in order to identify any demographic or outcome factors that may have been different between these groups.

Appendix Table 4.1.1 Pearson chi-square test results – subjects with VAP vs. subjects without VAP intention to treat analysis

ventilator associated pneumonia status by:	Value	df	p value
Gender	0.186	1	0.667
Race	4.139 [a]	2	0.126
History of presenting complaint	6.804 [b]	4	0.147
Chest injuries	4.092	1	0.043
Smoking history	8.057 [c]	3	0.045
Chronic sputum production	0.305 [d]	1	0.581
Respiratory history	3.899 [e]	3	0.273
Lobar collapse	0.106	1	0.744
Bronchoscopy	3.517 [f]	1	0.061
Re-ventilation	0.143 [g]	1	0.705
Antibiotics required	42.475	1	0.000
Re-admission to ICU	1.223 [h]	1	0.269
Mortality	1.699	1	0.192
Deceased in ICU	0.008 [i]	1	0.930

Number of Valid Cases = 144

a 3 cells (50.0%) have expected count less than 5. The minimum expected count is 1.38.
b 3 cells (30.0%) have expected count less than 5. The minimum expected count is 2.06.
c 3 cells (37.5%) have expected count less than 5. The minimum expected count is 0.45.
d 1 cells (25.0%) have expected count less than 5. The minimum expected count is 2.29.
e 3 cells (37.5%) have expected count less than 5. The minimum expected count is 1.60.
f 1 cells (25.0%) have expected count less than 5. The minimum expected count is 1.83.
g 1 cells (25.0%) have expected count less than 5. The minimum expected count is 4.35.
h 2 cells (50.0%) have expected count less than 5. The minimum expected count is 0.92.
i 2 cells (50.0%) have expected count less than 5. The minimum expected count is 1.91.

Appendix Table 4.1.2 Independent samples t-test results – subjects with VAP vs. subjects without VAP intention to treat analysis

Variable		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	p value	t	df	p value	Mean Difference	Std. Error Difference	Lower	Upper
age	Equal variances assumed	1.578	0.211	-2.550	142	0.012	-9.710	3.808	-17.239	-2.184
body mass index	Equal variances assumed	0.368	0.545	0.147	124	0.883	0.180	1.226	-2.246	2.606
Glasgow coma scale on admission to ICU	Equal variances assumed	0.487	0.486	-1.779	142	0.077	-0.690	0.388	-1.459	0.077
APACHE - worst score in first day	Equal variances assumed	0.048	0.826	0.130	140	0.897	0.150	1.120	-2.068	2.359
duration of MV (hrs)	Equal variances assumed	14.814	0.000	8.314	142	0.000	203.471	24.475	155.089	251.852
	Equal variances not assumed			6.282	38.552	0.000	203.471	32.389	137.933	269.009
length of ICU stay (hrs)	Equal variances assumed	6.475	0.012	7.360	142	0.000	195.434	26.553	142.944	247.924
	Equal variances not assumed			5.818	40.017	0.000	195.434	33.594	127.539	263.329
length of hospital stay (days)	Equal variances assumed	0.486	0.487	1.503	142	0.135	11.362	7.559	-3.582	26.305

Appendix 5 Summary Results of Economic Evaluation

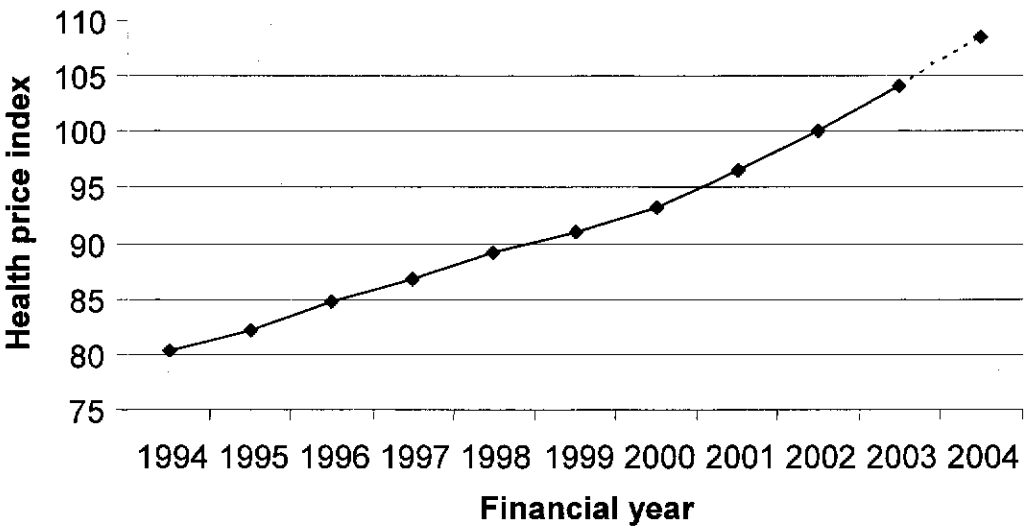
Appendix 5.1 Part A - Physiotherapy workload and costs data

Costs were determined for each individual subject. Summary physiotherapy workload and cost of intervention data of the 72 Part A Treatment Group 1 subjects are given in this section. Data are from the entire duration of MV for those subjects that did not have VAP, or until transfer to Part B of the study for those with VAP. Data are presented as occasions of service, time units and costs (Appendix Table 5.1.1) with summary data provided in Appendix Table 5.1.2. The total indexed respiratory physiotherapy costs from the 72 subjects in Part A Treatment Group 1 (Cost 1 of Figure 5.1) are given in Appendix Table 5.1.3. Comparison between ICU MV bed day costs for the Part A groups is in Appendix Table 5.1.4.

A 5.1.1 Health price index

A health price index for the financial year 2003/2004 had yet to be published at the time of conducting the economic analysis in September/October 2004. For the purpose of this study, health index deflators from the period 1993/1994 through to 2002/2003 (Australian Institute of Health and Welfare (AIHW) 2004) were graphed and then the curve of the graph was extrapolated to provide an estimate for the 2003/2004 year (Appendix Figure 5.1).

Based on this process, and using 2001/2002 as the reference year, an estimate of a health price index for 2003/2004 was determined to be 108.46; this value was subsequently used to index relevant costs in this study.



Appendix Figure 5.1 Graph of extrapolated health price index for 2003/2004

Appendix Table 5.1.1 Mean physiotherapy workload data and costs, shift by shift, for Part A

	Shift	Occasions of service	Time units (min)	Costs (AUD$)
Weekdays	Early	7.2 ± 6.0 5.5 0 – 24	225.4 ± 197.1 165.0 0 - 930	101 ± 88 74 0 – 415
	Evening	6.9 ± 5.5 5.5 0 - 26	206.7 ± 176.7 180.0 0 – 1065	104 ± 89 91 0 – 535
	Night	7.0 ± 5.8 5.5 0 – 23	211.0 ± 176.8 162.5 0 - 695	119 ± 100 92 0 – 392
	All	21.1 ± 16.4 17.0 0 - 72	641.9 ± 514.6 512.5 0 – 2595	323 ± 258 258 0 – 1,288
Saturday	Early	1.2 ± 1.5 1.0 0 – 6	35.0 ± 43.2 20.0 0 - 180	23 ± 29 13 0 – 121
	Evening	1.1 ± 1.2 1.0 0 – 4	24.6 ± 28.7 15.0 0 – 95	19 ± 22 12 0 – 73
	Night	0.9 ± 1.3 0.0 0 – 5	28.4 ± 37.8 0.0 0 – 145	22 ± 29 0 0 – 111
	All	3.3 ± 3.6 2.0 0 - 14	88.0 ± 98.9 70.0 0 – 400	64 ± 72 52 0 - 289
Sunday	Early	1.5 ± 1.6 1.5 0 – 6	39.6 ± 44.1 37.5 0 – 175	31 ± 34 29 0 – 137
	Evening	1.2 ± 1.4 1.0 0 – 5	27.8 ± 31.1 22.5 0 – 130	25 ± 28 20 0 – 116
	Night	1.2 ± 1.4 1.0 0 – 6	35.5 ± 41.0 32.5 0 – 170	32 ± 37 29 0 – 152
	All	3.9 ± 4.1 3.5 0 – 15	102.8 ± 107.9 92.5 0 – 450	88 ± 92 79 0 – 384

data are mean ± SD, followed by median, and range for 72 subjects
min = minutes; AUD$ = Australian dollars, rounded to the nearest dollar; SD = standard deviation; early shift (0700 – 1530), evening shift (1330 – 2200), and night shift (2130 – 0730).

Appendix Table 5.1.2 Part A summary physiotherapy workload data per subject

	Part A summary physiotherapy data
Weekday treatment duration (min) *	30.9 ± 5.7 18 – 49
Saturday treatment duration (min) *	27.0 ± 7.2 10 – 50
Sunday treatment duration (min) *	26.7 ± 5.9 10 – 50
Total occasions of service	28.3 ± 22.6 1 – 99
Total time units (min)	832.8 ± 675.2 45 – 3,375
Number of weekdays	4.9 ± 2.8 1 – 13
Number of Saturdays	0.8 ±0.7 0 – 3
Number of Sundays	0.9 ± .08 0 – 3
Number of treatment days	6.6 ± 4.0 1 – 18
Daily mean time units (min)	115.0 ± 39.0 38 – 209
Daily mean occasions of service	3.9 ± 1.2 1 – 6
Mean single treatment duration (min) *	30.0 ± 5.0 18 – 48

data are mean ± SD, then ranges for 72 subjects
min = minutes; AUD$ = Australian dollars, rounded to the nearest dollar; SD = standard deviation; ICU = intensive care unit; MV = mechanical ventilation; % = per cent
* = mean treatment duration per occasion of service

Appendix Table 5.1.3 Indexed Part A summary respiratory physiotherapy costs – Cost 1

Cost year (number of subjects)		Respiratory physiotherapy per subject costs			
		total	per day	per single treatment	as a per cent of ICU MV bed day cost
2000/2001 (n = 9)	Mean	609	69	16	1.77
	SD	442	21	2	0.85
	Sum	5,485	621	144	16.00
	Minimum	66	33	12	0.00
	Maximum	1,297	96	18	3.00
2001/2002 (n = 26)	Mean	450	57	16	1.55
	SD	380	20	4	0.63
	Sum	11,693	1,486	409	40.00
	Minimum	66	20	11	0.00
	Maximum	1,376	96	34	3.00
2002/2003 (n = 31)	Mean	544	73	19	1.53
	SD	410	26	3	0.70
	Sum	8,706	1,175	297	25.00
	Minimum	26	26	14	0.00
	Maximum	1,457	121	26	2.00
2003/2004 (n = 43)	Mean	437	74	20	1.95
	SD	407	26	3	0.70
	Sum	9,185	1,551	414	41.00
	Minimum	97	30	16	1.00
	Maximum	2,074	115	25	3.00
Total (n = 72)	Mean	487	67	18	1.69
	SD	399	24	4	0.70
	Sum	35,069	4,834	1,264	122.00
	Minimum	26	20	11	0.00
	Maximum	2,074	121	34	3.00

data are Australian dollars, rounded to the nearest dollar; ICU = intensive care unit; MV = mechanical ventilation; n = number; $ = Australian dollars; SD = standard deviation

Appendix Table 5.1.4 Indexed summary costs for ICU MV bed day cost per subject, as per Part A group allocation

		Part A		Total ICU MV bed day costs for all subjects
Cost year	Parameter	Treatment Group 1	Control Group 2	
2000/2001	Number	9	7	16
	Mean	40,342	51,465	45,209
	SD	29,168	34,230	30,902
	Sum	363,082	360,257	723,340
	Minimum	5,232	23,169	5,233
	Maximum	103,677	122,458	122,459
2001/2002	Number	26	28	54
	Mean	29,323	34,863	32,195
	SD	20,994	26,169	23,761
	Sum	762,397	976,157	1,738,556
	Minimum	2,893	5,900	2,893
	Maximum	71,070	109,312	109,314
2002/2003	Number	16	15	31
	Mean	35,411	35,946	35,670
	SD	16,972	32,535	25,260
	Sum	566,576	539,193	1,105,770
	Minimum	6,5349	8,234	6,535
	Maximum	59,864	118,539	118,540
2003/2004	Number	21	22	43
	Mean	23,558	33,835	28,816
	SD	16,902	34,639	27,622
	Sum	494,715	744,371	1,239,086
	Minimum	4,474	4,940	4,475
	Maximum	77,745	133,440	133,440
Total	Number	72	72	144
	Mean	30,372	36,389	33,380
	SD	20,612	30,797	26,286
	Sum	2,186,771	2,619,978	4,806,748
	Minimum	2,893	4,940	2,893
	Maximum	103,677	133,440	133,440

data are Australian dollars, rounded to the nearest dollar; ICU = intensive care unit; MV = mechanical ventilation; SD = standard deviation

Appendix Table 5.1.5 Indexed Part A summary respiratory physiotherapy costs for 14 Treatment Group 1 subjects with VAP

Cost year (number of subjects)		Respiratory physiotherapy per subject costs			
		total	per day	per single treatment	as a per cent of ICU MV bed day cost
2000/2001 (n = 2)	Mean	452	58	16	0.47
	SD	547	36	1	0.48
	Sum	904	117	32	1.00
	Minimum	66	33	15	0.00
	Maximum	839	84	16	1.00
2001/2002 (n = 5)	Mean	440	67	15	0.80
	SD	305	6	1	0.39
	Sum	2,199	333	76	4.00
	Minimum	66	58	14	0.00
	Maximum	745	74	17	1.00
2002/2003 (n = 4)	Mean	295	77	23	0.55
	SD	250	40	3	0.40
	Sum	1,180	308	91	2.00
	Minimum	26	26	20	0.00
	Maximum	615	115	26	1.00
2003/2004 (n = 3)	Mean	410	86	18	1.06
	SD	185	15	1	0.42
	Sum	1,229	259	53	3.00
	Minimum	253	72	17	1.00
	Maximum	614	102	19	1.00
Total (n = 14)	Mean	394	73	18	0.74
	SD	275	25	4	0.42
	Sum	5,512	1,018	251	10.00
	Minimum	26	26	14	0.00
	Maximum	839	115	26	1.00

data are Australian dollars, rounded to the nearest dollar; ICU = intensive care unit; MV = mechanical ventilation; n = number; SD = standard deviation

Appendix 5.2 Part B - Physiotherapy workload and costs data

Summary physiotherapy workload and cost of intervention data of the 17 Part B Treatment Group 3 subjects only are given in this section. Respiratory physiotherapy data are only from the duration subjects were in Part B of the study, and do include data from the time period in Part A prior to transfer to Part B. Data are presented as occasions of service, time units and costs (Appendix Table 5.2.1) with summary data provided in Appendix Table 5.2.2.

Appendix Table 5.2.1 Mean physiotherapy workload data and costs, shift by shift, for Part B

	Shift	Occasions of service	Time units (min)	Costs (AUD$)
Weekdays	Early	13.9 ± 11.4 10.0 4 – 53	461.8 ± 454.9 335.0 120 - 2070	206 ± 203 150 54 – 924
	Evening	11.9 ± 8.6 10.0 2 - 39	362.4 ± 305.0 345.0 90 – 1385	182 ± 153 173 45 – 695
	Night	10.5 ± 9.5 8.0 2 – 43	315.3 ± 272.2 250.0 60 – 1,240	178 ± 153 141 34 – 699
	All	36.3 ± 28.8 29.0 8 - 135	1139.4 ± 1014.2 915.0 3,000 – 4,695	567 ± 500 457 148 – 2,318
Saturday	Early	2.4 ± 1.9 2.0 0 – 7	61.8 ± 55.4 55.0 0 - 205	41 ± 37 37 0 – 137
	Evening	1.6 ± 1.8 1.0 0 – 6	35.6 ± 38.7 25.0 0 – 135	27± 30 19 0 – 104
	Night	1.4 ± 1.9 1.0 0 – 4	39.1 ± 49.8 30.0 0 – 205	30 ± 38 23 0 – 157
	All	5.4 ± 5.3 5.0 0 - 21	136.5 ± 136.1 120.0 0 – 545	99 ± 99 83 0 – 398
Sunday	Early	1.9 ± 2.2 2.0 0 – 9	58.2 ± 64.6 50.0 0 – 260	45 ± 50 39 0 – 203
	Evening	1.8 ± 1.8 2.0 0 – 7	44.3 ± 39.5 40.0 0 – 155	40 ± 35 36 0 – 139
	Night	1.8 ± 2.0 2.0 0 – 8	47.9 ± 49.9 50.0 0 – 205	43 ± 45 45 0 – 184
	All	5.5 ± 5.5 5.0 0 – 24	150.5 ± 142.8 145.0 0 – 620	128 ± 121 125 0 – 526

data are mean ± SD, followed by median, and range
min = minutes; AUD$ = Australian dollars, rounded to the nearest dollar; SD = standard deviation; early shift (0700 – 1530), evening shift (1330 – 2200), and night shift (2130 – 0730).

Appendix Table 5.2.2 Part B summary physiotherapy workload data and costs

	Part B summary physiotherapy data
Weekday treatment duration (min) *	30.7 ± 4.0 21 - 39
Saturday treatment duration (min) *	24.8 ± 4.3 18 – 35
Sunday treatment duration (min) *	28.2 ± 4.6 23 - 37
Total occasions of service	47.2 ±39.0 8 – 180
Total time units (min)	1,426.3 ± 1,274.4 310 – 586.0
Number of weekdays	7.6 ± 4.8 2 – 21
Number of Saturdays	1.4 ± 1.1 0 – 4
Number of Sundays	1.2 ± .1.0 0 – 4
Total number of treatment days	10.1 ± 6.6 2 – 29
Daily mean time units (min)	135.6 ± 33.4 51 – 202
Daily mean occasions of service	4.5 ± 1.0 2 – 6
Mean single treatment duration (min) *	30.0 ± 3.8 22.2 – 38.8

data are mean ± SD, then range
* = mean treatment duration per occasion of service
min = minutes; SD = standard deviation; ICU = intensive care unit; MV = mechanical ventilation; % = per cent

A 5.2.2 Indexed Part B summary respiratory physiotherapy costs

Individual subject cost data were indexed prior to summation. These summary respiratory physiotherapy costs are from the 17 Part B subjects randomised to Treatment Group 3 and represent Cost 2 and Cost 3 of Figure 5.1 (Appendix Table 5.2.3), whilst the ICU MV bed day costs are from all 33 Part B subjects (Appendix Table 5.2.4).

Appendix Table 5.2.3 Indexed Part B summary respiratory physiotherapy costs – Cost 2 & Cost 3

Cost year (number of subjects)		Respiratory physiotherapy per subject costs			
		total	per day	per single treatment	as a per cent of ICU MV bed day cost
2000/2001 (n = 5)	Mean	1,295	81	16	2.04
	SD	1,073	18	1	0.45
	Sum	6,476	406	79	10.00
	Minimum	301	59	14	1.00
	Maximum	3,133	108	17	3.00
2001/2002 (n = 6)	Mean	556	73	16	1.76
	SD	203	11	1	0.26
	Sum	3,337	436	95	11.00
	Minimum	246	61	13	1.00
	Maximum	864	86	18	2.00
2002/2003 (n = 5)	Mean	676	80	19	1.87
	SD	393	17	1	0.40
	Sum	3,380	401	94	9.00
	Minimum	157	62	18	1.00
	Maximum	1,234	108	20	3.00
2003/2004 (n = 1)	Mean	205	29	13	0.65
	SD	0	0	0	0.00
	Sum	205	29	3	1.00
	Minimum	205	29	3	1.00
	Maximum	205	29	3	1.00
Total (n = 17)	Mean	788	75	17	1.81
	SD	682	18	2	0.46
	Sum	13,398	1,272	281	31.00
	Minimum	157	29	13	1.00
	Maximum	3,133	108	20	3.00

data are Australian dollars, rounded to the nearest dollar; ICU = intensive care unit; MV = mechanical ventilation; n = number; SD = standard deviation

Appendix Table 5.2.4 Indexed summary costs for ICU MV bed day cost for Part B subjects, as per group allocation

		Part B subjects		Total ICU MV bed day costs for Part B subjects
Cost year	Parameter	Treatment Group 3	Control Group 4	
2000/2001	Number	5	5	10
	Mean	59,790	36,671	48,230
	SD	36,423	24,474	31,691
	Sum	298,949	183,355	482,304
	Minimum	15,944	15,944	15,944
	Maximum	115,594	75,734	115,594
2001/2002	Number	6	4	10
	Mean	30,938	35,062	32,588
	SD	8,146	20,625	13,535
	Sum	185,625	140,250	325,875
	Minimum	16,500	8,250	8,250
	Maximum	41,250	57,750	57,750
2002/2003	Number	5	5	10
	Mean	38,666	49,836	44,251
	SD	28,659	26,238	26,565
	Sum	193,328	249,179	442,507
	Minimum	8,592	25,777	8,592
	Maximum	85,924	94,516	94,516
2003/2004	Number	1	2	3
	Mean	31,318	82,769	65,618
	SD	0	53,781	48,255
	Sum	31,318	165,537	196,855
	Minimum	31,318	44,740	31,318
	Maximum	31,318	120,797	120,797
Total	Number	17	16	33
	Mean	41,719	46,145	43,865
	SD	26,703	29,449	27,715
	Sum	709,220	738,321	1,447,542
	Minimum	8,592	8,250	8,250
	Maximum	115,594	120,797	120,797

data are Australian dollars, rounded to the nearest dollar; ICU = intensive care unit; MV = mechanical ventilation; SD = standard deviation

Appendix 5.3 Subjects with and without VAP - Physiotherapy workload and costs data

The following section provides physiotherapy workload data comparison between those subjects with and without VAP, based on intention to treat philosophy. For non-VAP and VAP subjects, data are from the entire duration of MV. Data are presented as occasions of service (Appendix Table 5.3.1), time units (Appendix Table 5.3.2) and costs (Appendix Table 5.3.3) from those randomised to receive respiratory physiotherapy. As normality and variance assumptions were not met, a nonparametric test in the form of the Mann-Whitney U test was used to compare the non-VAP and VAP subjects, results of which form the basis of this section.

A 5.3.1 Respiratory physiotherapy workload and cost determination for subjects with and without VAP

There were 144 subjects enrolled into this study, of which 58 received respiratory physiotherapy treatment and did not develop VAP (Cost 4, Figure 5.1) (Appendix Table 5.3.4). Of the remaining 86 subjects, 53 did not receive respiratory physiotherapy and did not develop VAP. The summary indexed ICU MV bed day costs associated with this subset of subjects (Cost 5 of Figure 5.1) is detailed in Appendix Table 5.3.5. From the remaining 33 subjects who developed VAP, 17 received respiratory physiotherapy in Part B, represented by Cost 2 and Cost 3 of Figure 5.1 (Appendix Table 5.2.3). Due to the re-randomisation and potential cross-over between Treatment and Control Groups from Part A to Part B, 20 of the 33 Part B subjects received some respiratory physiotherapy during their MV, either in Part A alone, Part B alone, or during both phases of the study. Total costs for these 20 subjects are reported in Appendix Table 5.3.6. The overall summary of indexed ICU MV bed day costs for those subjects with and without VAP is given in Appendix Table 5.3.7. Finally for those subjects with and without VAP, indexed summary costs for ICU MV bed day cost per subject, as per Part A group allocation, is provided in Appendix Table 5.3.8.

A 5.3.2 Occasions of service

Significant differences between occasions of service for the non-VAP and VAP groups were evident (Appendix Table 5.3.1), with those subjects with VAP being either reviewed or treated by a physiotherapist more often.

Appendix Table 5.3.1 Mean physiotherapy occasion of service workload data, shift by shift, comparing subjects with and without VAP

	Shift	Non-VAP subjects (n = 58)	VAP subjects (n = 20)	p value
Weekdays	Early	6.4 ± 5.4 5.0 0 – 24	18.0 ± 10.0 15.0 6 - 55	<0.01
	Evening	5.6 ± 5.0 4.0 0 - 26	14.2 ± 7.9 13.0 2 - 40	<0.01
	Night	5.2 ± 5.2 3.0 0 – 23	15.9 ± 18.9 13.0 1 - 111	<0.01
	All	17.1 ± 14.8 13.0 0 - 72	48.2 ± 29.7 44.0 11 - 143	<0.01
Saturday	Early	1.1 ± 1.3 1.0 0 – 6	2.8 ± 1.9 3.0 0 - 7	<0.01
	Evening	0.9 ± 1.1 0.0 0 – 4	2.3 ± 1.7 2.0 0 - 6	<0.01
	Night	0.8 ± 1.2 0.0 0 – 5	2.1 ± 1.7 2.0 0 - 8	<0.01
	All	2.9 ± 3.3 2.0 0 - 14	7.1 ± 4.7 7.0 0 - 21	<0.01
Sunday	Early	1.3 ± 1.4 1.0 0 – 6	2.7 ± 1.9 2.0 0 - 10	<0.01
	Evening	1.0 ± 1.2 1.0 0 – 4	2.4 ± 1.8 2.0 0 - 7	<0.01
	Night	0.9 ± 1.2 0.0 0 – 6	2.3 ± 1.8 2.0 0 - 8	<0.01
	All	3.2 ± 3.5 3.0 0 – 15	7.4 ± 4.9 6.0 0 - 25	<0.01

data are mean ± SD, followed by median, and range
n = number; p = probability; SD = standard deviation; early shift (0700 – 1530), evening shift (1330 – 2200), and night shift (2130 – 0730).

A 5.3.3 Time units

A similar result to the occasions of service comparison between subjects with and without VAP was found with physiotherapy time units. Significant differences between time units for the groups were evident (Table 5.3.2), with subjects with VAP receiving a greater duration of physiotherapy intervention.

Appendix Table 5.3.2 Mean physiotherapy time unit workload data, shift by shift, comparing subjects with and without VAP

	Shift	Non-VAP subjects (n = 58)	VAP subjects (n = 20)	p value
Weekdays	Early	181.4 ± 176.1 120.0 0 - 930	553.2 ± 372.9 440.0 140 – 2,120	<0.01
	Evening	157.2 ± 161.1 115.0 0 – 1,065	400.9 ± 260.7 395.0 0 - 500	<0.01
	Night	151.0 ± 162.2 90.0 0 - 695	373.6 ± 247.6 340.0 30 – 1,295	<0.01
	All	488.9 ± 469.0 345.0 0 – 2,595	1,327.7 ± 822.8 1,295.0 250 – 4,830	<0.01
Saturday	Early	31.0 ± 37.7 20.0 0 - 180	78.9 ± 57.0 75.0 0 - 205	<0.01
	Evening	18.7 ± 26.3 0.0 0 – 110	47.4 ± 37.4 45.0 0 - 135	<0.01
	Night	23.2 ± 33.6 0.0 0 – 145	53.0 ± 44.1 50.0 0 - 205	<0.01
	All	72.9 ± 88.8 40.0 0 – 400	177.0 ± 119.2 170.0 0 - 545	<0.01
Sunday	Early	33.4 ± 38.9 25.0 0 – 175	74.1 ± 52.9 60.0 0 - 280	<0.01
	Evening	21.1 ± 26.9 10.0 0 – 130	51.0 ± 40.1 45.0 0 - 155	<0.01
	Night	25.4 ± 36.0 0.0 0 – 170	60.2 ± 49.7 50.0 0 - 205	<0.01
	All	79.9 ± 93.2 55.0 0 – 450	185.2 ± 127.5 175.0 0 - 640	<0.01

data are mean ± SD, followed by median, and range, in minutes
n = number; p = probability; SD = standard deviation; early shift (0700 – 1530), evening shift (1330 – 2200), and night shift (2130 – 0730).

Appendix Table 5.3.3 Mean physiotherapy summary workload data, comparing subjects with and without VAP

	Non-VAP subjects (n = 58)	VAP subjects (n = 20)	p value
Weekday treatment duration (min) *	27.8 ± 6.1 17 - 49	28.1 ± 4.9 11 - 35	0.39
Saturday treatment duration (min) *	25.3 ± 7.5 10 – 50	24.5 ± 3.4 18 - 35	0.39
Sunday treatment duration (min) *	24.0 ± 7.5 5 - 50	24.2 ± 6.1 5 - 37	0.90
Total occasions of service	23.2 ± 20.4 2 – 99	62.7 ± 37.4 12 - 186	<0.01
Total time units (min)	641.6 ± 615.4 55 – 3,375	1,689.9 ± 1,044.4 255 – 6,015	<0.01
Number of weekdays	4.9 ± 3.0 1 – 14	11.2 ± 5.0 4 – 23	<0.01
Number of Saturdays	0.9 ± 0.8 0 – 3	2.1 ± 1.2 0 - 5	<0.01
Number of Sundays	1.0 ± 0.8 0 – 3	2.2 ± 1.2 0 - 5	<0.01
Total number of treatment days	6.8 ± 4.2 2 – 20	15.4 ± 7.4 5 – 32	<0.01
Daily mean time units (min)	86.1 ± 41.4 26 – 209	111.0 ± 37.0 48 - 188	<0.01
Daily mean occasions of service	3.1 ± 1.2 1 – 6	4.2 ± 1.9 2 – 13	<0.01
Daily mean treatment duration (min) *	26.9 ± 5.3 18 – 48	27.2 ± 4.4 13 – 34	0.39

data are mean ± SD, then range
min = minutes; n = number; p = probability; SD = standard deviation.
* = mean treatment duration per occasion of service

A 5.3.4 Indexed summary costs for the 58 non-VAP subjects from Part A Treatment Group 1

Total respiratory physiotherapy costs and total ICU MV bed day costs were calculated individually for each of the 58 subjects from Part A Treatment Group 1 that received respiratory physiotherapy but did not develop VAP (Cost 4 from Figure 5.1), and are summarised in Appendix Table 5.3.4.

Appendix Table 5.3.4 Indexed summary costs for the 58 non-VAP subjects from Part A Treatment Group 1 – Cost 4

Cost year (number of subjects)		Respiratory physiotherapy per subject costs				Total ICU MV bed day costs per subject
		total	per day	per single treatment	as a per cent of ICU MV bed day cost	
2000/2001 (n = 7)	Mean	654	72	16	2.15	29,667
	SD	448	17	2	0.43	17,642
	Sum	4,580	504	112	15.00	207,670
	Minimum	133	52	12	2.00	5,232
	Maximum	1,297	96	18	3.00	53,479
2001/2002 (n = 21)	Mean	452	55	16	1.73	24,747
	SD	403	21	5	0.54	18,866
	Sum	9,494	1,153	334	36.00	519,681
	Minimum	68	20	11	1.00	2,893
	Maximum	1,376	96	34	3.00	71,070
2002/2003 (n = 12)	Mean	627	72	17	1.86	31,252
	SD	427	22	2	0.39	16,945
	Sum	7,526	867	206	22.00	375,021
	Minimum	101	41	14	1.00	6,534
	Maximum	1,457	121	20	2.00	59,864
2003/2004 (n = 18)	Mean	442	72	20	2.10	20,767
	SD	436	27	3	0.62	16,066
	Sum	7,956	1,292	361	38.00	373,810
	Minimum	97	30	16	1.00	4,474
	Maximum	2,074	115	25	3.00	77,745
Total (n = 58)	Mean	510	66	17	1.92	25,451
	SD	422	24	4	.55	17,505
	Sum	29,556	3,816	1,013	111.00	1,476,182
	Minimum	68	20	11	1.00	2,893
	Maximum	2,074	121	34	3.00	77,745

data are Australian dollars, rounded to the nearest dollar; ICU = intensive care unit; MV = mechanical ventilation; SD = standard deviation

A 5.3.5 Indexed summary costs for the 53 non-VAP subjects from Part A Control Group 2

Total ICU MV bed day costs were calculated individually for each of the 53 subjects from the Part A Control Group 2 that did not develop VAP. These figures, as summarised in Appendix Table 5.3.5, were used to determine Cost 5 of Figure 5.1.

Appendix Table 5.3.5 Indexed summary costs for the 53 non-VAP subjects from Part A Control Group 2 – Cost 5

Cost year (number of subjects)		total ICU MV bed day costs per subject
2000/2001 (n = 4)	Mean	43,022
	SD	18,361
	Sum	172,087
	Minimum	23,169
	Maximum	63,776
2001/2002 (n = 21)	Mean	27,123
	SD	16,896
	Sum	569,573
	Minimum	5,900
	Maximum	73,219
2002/2003 (n = 12)	Mean	24,941
	SD	21,801
	Sum	299,287
	Minimum	8,234
	Maximum	77,197
2003/2004 (n = 16)	Mean	17,099
	SD	14,412
	Sum	273,587
	Minimum	4,940
	Maximum	55,552
Total (n = 53)	Mean	24,803
	SD	18,322
	Sum	1,314,534
	Minimum	4,940
	Maximum	77,197

data are Australian dollars, rounded to the nearest dollar; ICU = intensive care unit; MV = mechanical ventilation; SD = standard deviation

Appendix Table 5.3.6 Indexed summary costs for the 20 VAP subjects who received any respiratory physiotherapy

Cost year (number of subjects)		Respiratory physiotherapy per subject costs				Total ICU MV bed day costs per subject
		total	per day	per single treatment	as a per cent of ICU MV bed day cost	
2000/2001 (n = 4)	Mean	1,733	79	16	2.02	82,775
	SD	1,020	20	1	0.39	35,815
	Sum	6,930	316	641	8.07	331,099
	Minimum	895	64	151	1.68	51,735
	Maximum	3,133	108	171	2.56	122,458
2001/2002 (n = 6)	Mean	808	73	15	1.64	53,157
	SD	414	8	1	0.49	34,177
	Sum	4,846	435	91	9.86	318,943
	Minimum	246	61	14	0.99	17,359
	Maximum	1,296	83	17	2.18	109,313
2002/2003 (n = 6)	Mean	968	78	19	1.78	56,151
	SD	272	12	1	0.39	19,274
	Sum	5,807	465	113	10.66	336,909
	Minimum	703	62	18	1.35	36,518
	Maximum	1,244	96	20	2.32	91,473
2003/2004 (n = 4)	Mean	747	77	14	1.81	41,202
	SD	466	35	5	0.91	10,862
	Sum	2,987	310	57	7.25	164,806
	Minimum	205	29	8	0.47	25,865
	Maximum	1,218	104	18	2.39	51,497
Total (n = 20)	Mean	1,029	76	16	1.79	57,588
	SD	633	18	3	0.52	28,692
	Sum	20,570	1,526	325	35.85	1,151,758
	Minimum	205	29	8	0.47	17,359
	Maximum	3,133	108	20	2.56	122,458

data are Australian dollars, rounded to the nearest dollar; ICU = intensive care unit; MV = mechanical ventilation; SD = standard deviation

A 5.3.6 Indexed summary costs for the 111 non-VAP subjects

Total ICU MV bed day costs were calculated individually for each of the 111 subjects that did not develop VAP (Cost 4 and Cost 5 from figure 5.1) and are summarised in Appendix Table 5.3.7.

Appendix Table 5.3.7 Indexed summary ICU MV bed day costs for subjects with and without VAP

		Subject VAP status		Total ICU MV bed day costs
Cost year	Parameter	Non-VAP	VAP	
2000/2001	Number	11	5	16
	Mean	34,523	68,716	45,209
	SD	18,256	41,749	30,902
	Sum	379,757	343,582	723,339
	Minimum	5,232	32,081	5,232
	Maximum	63,776	122,458	122,458
2001/2002	Number	42	12	54
	Mean	25,935	54,108	32,195
	SD	17,730	29,582	23,761
	Sum	1,089,254	649,301	1,738,555
	Minimum	2,893	15,512	2,893
	Maximum	73,219	109,312	109,312
2002/2003	Number	24	7	31
	Mean	28,096	61,637	35,670
	SD	19,365	27,141	25,260
	Sum	674,308	431,461	1,105,769
	Minimum	6,534	36,518	6,534
	Maximum	77,197	118,539	118,539
2003/2004	Number	34	9	43
	Mean	19,041	65,743	28,816
	SD	15,194	33,366	27,622
	Sum	647,397	591,689	1,239,086
	Minimum	4,474	25,865	4,474
	Maximum	77,745	133,440	133,440
Total	Number	111	33	144
	Mean	25,142	61,092	33,380
	SD	17,821	31,123	26,286
	Sum	2,790,716	2,016,032	4,806,748
	Minimum	2,893	15,512	2,893
	Maximum	77,745	133,440	133,440

data are Australian dollars, rounded to the nearest dollar; ICU = intensive care unit; MV = mechanical ventilation; VAP = ventilator associated pneumonia; SD = standard deviation

A 5.3.7 Indexed summary costs for all subjects

Total ICU MV bed day costs were calculated individually for each of the 144 subjects included in this study and are summarised as per Part A group allocation (Appendix Table 5.3.8).

Appendix Table 5.3.8 Indexed summary costs for ICU MV bed day cost per subject, as per Part A group allocation

Cost year	Parameter	Part A subjects with VAP		Part A subjects without VAP	
		Treatment Group 1	Control Group 2	Treatment Group 1	Control Group 2
2000/2001	Number	2	3	7	4
	Mean	77,706	62,723	29,667	43,022
	SD	36,729	51,737	17,642	18,362
	Sum	155,412	188,170	207,670	172,087
	Minimum	51,735	32,081	5,232	23,169
	Maximum	103,677	122,458	53,479	63,776
2001/2002	Number	5	7	21	21
	Mean	48,543	58,083	24,747	27,123
	SD	20,083	35,933	18,866	16,896
	Sum	242,717	406,584	519,681	569,573
	Minimum	17,359	15,512	2,893	5,900
	Maximum	68,264	109,312	71,070	73,2195
2002/2003	Number	4	3	12	12
	Mean	47,889	79,969	31,252	24,941
	SD	10,514	34,088	16,945	21,801
	Sum	191,554	239,906	375,021	299,287
	Minimum	36,518	53,881	6,534	8,234
	Maximum	59,416	118,539	59,864	77,197
2003/2004	Number	3	6	18	16
	Mean	40,302	78,464	20,767	17,099
	SD	13,120	33,614	16,066	14,412
	Sum	120,905	470,783	373,810	273,587
	Minimum	25,865	43,901	4,474	4,940
	Maximum	51,497	133,440	77,745	55,552
Total	Number	14	19	58	53
	Mean	50,756	68,708	25,451	24,803
	SD	20,524	35,686	17,505	18,322
	Sum	710,589	1,305,444	1,476,182	1,314,534
	Minimum	17,359	15,512	2,893	4,940
	Maximum	103,677	133,440	77,745	77,197

Data are Australian dollars, rounded to the nearest dollar; ICU = intensive care unit; MV = mechanical ventilation; VAP = ventilator associated pneumonia; SD = standard deviation