The Efficient Measurement of Resource Utilisation in Clinical Trials in Critical Care

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I declare that the research presented here is my own original work and has not been submitted to any other institution for the award of a degree.

Signed: .....

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1 Synopsis

Background:

Clinical trials are necessary to ensure that costly new therapies are effective, and it is equally important that economic analyses accompany clinical trials to ensure that new therapies are not only effective, but are also cost effective. To perform an economic analysis requires the collection of data to estimate the resources consumed in the delivery of the therapies being examined in the clinical trial. This may be a problem for researchers as the data necessary to accurately estimate resource utilisation in clinical trials in critical care is burdensome to collect. Of the direct approaches to the collection of data, the bottom-up methods are rarely used because of the complexity and burden of the data collection. Top-down methods lack the precision that would allow widespread use. Other methods of estimating resource utilisation, such as the Intensive Care Unit (ICU) length of stay and instruments to estimate workload such as the Therapeutic Intervention Scoring System (TISS) score, have been employed to reduce the burden of data collection.

The simplest measure of resource utilisation in intensive care is ICU length of stay. While ICU length of stay has been advocated as a valid measure to estimate resource utilisation, its use has been questioned, particularly with regards to its precision. The TISS score is purported to offer a significant advantage in increased precision of estimating resource utilisation in critical care. However, the collection of all data necessary to calculate the TISS score is time consuming, and in the context of conducting a clinical trial, is also costly. It is currently not known whether resource

utilisation in critical care could be estimated more efficiently while retaining acceptable precision.

The aim of this study was to compare the accuracy of the estimation of resource utilisation using various methods applied to a comprehensive database of TISS scores and total ICU resource utilisation as measured by total ICU costs.

Methods:

The data for this analysis was collected in the Medical Intensive Care Unit at the University of Aachen Hospital from March 7, 2001 until March 7 2002. Data were collected on each patient regarding basic demographics, severity of illness, ICU length of stay, and hospital outcomes. Data were also collected to allow calculation of the TISS score each day in the ICU. The daily scores were summed to give a total TISS score for the ICU admission. Resource utilisation for each patient was measured using a combination of a top-down approach for hoteling costs, support staff, staff overheads, and central hospital costs. Patient specific resource use was measured directly for each patient. Total resource use was measured by summing the total costs for each patient over the entire ICU stay.

Linear regression was used to describe the relationship between ICU length of stay and total ICU costs and between total TISS-28 score and total ICU costs. Further, a parsimonious model was developed by first performing bivariate linear regression with total ICU costs as the dependent variable, and ICU length of stay and each of the TISS components as the independent variables. TISS components that did not add information above that of the ICU length of stay were eliminated from further consideration. The remaining TISS-28 components that were present in >2% of

patients, were considered for inclusion in a multi-variate regression model. Backwards-stepwise elimination of candidate variables was performed, utilising variance inflation factors and condition numbers to arrive at a final stable parsimonious model.

The regression models to predict costs using ICU length of stay, the total TISS-28 score and the final parsimonious model were compared using adjusted R^2 values and their 95% confidence limits.

Results:

There were 729 patients included in the analysis, the mean (SD) age was 66 (14.2) years, 28.5% were female and the mean (SD) SAPS II score was 31.0 (18.2). The most common admission diagnoses were related to cardiovascular diseases. The mortality in the ICU was 10.2% and hospital mortality in the cohort was 13.9%. The median TISS-28 (IQR) score was 40 (24-83) and the median (IQR) total costs of ICU stay was €2177 (€1241-€3894). Simple linear regression demonstrated a significant relationship between ICU length of stay and total ICU costs ($F=2480$, $p<0.0005$, $R^2=0.773$). There was also a significant relationship between total TISS-28 points and total ICU costs ($F=3497$, $p<0.0005$, $R^2=0.828$). Assessment for collinearity revealed significant collinearity between TISS components. A parsimonious model was developed with 9 TISS elements remaining; intervention outside ICU, supplementary ventilation, care of artificial airways, single vasoactive medication, multiple vasoactive medications, pulmonary artery catheter, multiple ICU interventions, single ICU intervention and active diuresis. The parsimonious regression model showed a significant relationship between the 9 TISS components and total ICU costs ($F=560$, $p<0.0005$, $R^2=0.875$). Assessment of the 95%

confidence limits of the adjusted R^2 values revealed that the parsimonious model was significantly better at predicting total ICU costs, while using only a fraction of the data of the full TISS-28.

Conclusion:

This study has demonstrated that resource utilisation in critical care can be estimated with improved efficiency, as well as improved precision, with the collection of only 9 of the components of the full TISS-28 score. These 9 components also estimate resource utilisation with greater precision than ICU length of stay. Researchers in critical care, who are contemplating conducting an economic analysis alongside a clinical trial should consider collecting these 9 data elements to facilitate the estimation of resource utilisation.

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6 List of abbreviations

ARDS	Acute Respiratory Distress Syndrome
CRASH	Corticosteroid Randomisation After Significant Head injury
DRG	Diagnosis Related Group
ECMO	Extracorporeal Membrane Oxygenation
EGDT	Early Goal Directed Therapy
GDP	Gross Domestic Product
HMO	Health management organisation
ICU	Intensive Care Unit
IQR	Interquartile range
IV	Intravenous
LOS	Length of Stay
MPM	Mortality Prediction Model
NEMS	Nine Equivalents of Nursing Manpower Score
NHS	National Health Service
NT-pro-BNP	N Terminal pro brain natureitic peptide
QALY	Quality Adjusted Life Year
RVU	Relative Value Unit

SAPS II	Simplified Acute Physiological Score version II
SD	Standard Deviation
TISS	Therapeutic intervention Scoring System
USA	United States of America

7 Introduction

7.1 Background

The cost of modern clinical trials is daunting (1). Estimates of the current cost of performing modern clinical trials can exceed hundreds of millions of dollars (2). This is a significant problem as large clinical trials are necessary to demonstrate that new interventions provide improved health outcomes (3). This is particularly so in Intensive Care, as providing intensive care treatments consume a significant and increasing proportion of the healthcare budget (4). As there is a limit to the resources within any healthcare system, it is imperative that intensive care interventions are demonstrated to be not only efficacious, but also provide good value for money, so that the scarce resources are allocated in a manner most likely to provide the greatest benefit to society. This assessment of new therapies is known as economic analysis and can take a number of forms; a cost-minimisation analysis, a cost-benefit analysis, a cost-effectiveness analysis, or a cost-utility analysis. The reference standard for performing an economic analysis of a new therapy in critical care is to perform a cost-utility analysis in conjunction with the clinical trial assessing the clinical effectiveness of the therapy. In order to perform this type of study, all of the resources consumed in the delivery of the therapies being assessed are measured and compared to the benefits conferred by the treatments.

Just as overall healthcare resources are limited, so are the resources available to perform clinical research. One of the issues in performing economic analyses is the expense. The cost of performing a clinical trial for a new therapy can be prohibitive. The additional expense of performing a thorough economic evaluation alongside the clinical trial may be beyond the resources of many investigators. This is because, in order to perform a thorough economic analysis, all the resources utilised in the course of a trial participant's treatment need to be recorded. Regardless of which method of collecting data to estimate resource utilisation is used, the collection of this data is a significant additional expense for the clinical researcher. Costing data can be collected in a ground-up method, allocated in a top-down approach, patient charges can be used as a surrogate for costs, or some composite of all these approaches may be utilised. Another approach is to use an alternative method to estimate resource utilisation, such as Intensive Care Unit (ICU) length of stay, or an instrument used to measure workload, the most commonly used of these instruments is the Therapeutic Intervention Scoring System (TISS) (5, 6). Each of these approaches has significant limitations in terms of the workload for researchers and the precision of the estimates of resources utilisation.

A method for the collection of data related to resource utilisation in clinical trials that was more efficient than existing methods, while retaining acceptable precision, would offer significant advantages to researchers attempting to perform economic analyses in conjunction with clinical trials in critical care.

7.1.1 The costs of performing clinical trials

In order to adequately assess new and sometimes existing therapies, robust evidence that has minimum of bias and random error is required (3). This generally means evidence from adequately powered, usually very large, methodologically sound, randomised clinical trials (7). In the field of intensive care this has been clearly demonstrated in the case of the use of corticosteroids for the treatment of acute traumatic brain injury.

Traumatic brain injury is responsible for the deaths of many millions of people each year, with many more left with severe permanent disability (8). While much of the neurological damage occurs at the time of injury, post-traumatic inflammation was also considered to be an important component of the pathophysiology of the disease (9). As such corticosteroids were used for many years to treat patients with traumatic brain injury. Small studies and a meta-analysis were unable to confirm nor refute a significant benefit associated with the use of corticosteroids for patients with acute traumatic brain injury (10). A subsequent randomised controlled trial with 10,000 participants, the CRASH trial, demonstrated a significant increase in mortality associated with the use of corticosteroids (11). Subsequent to this, international guidelines for the management of traumatic brain injury have included recommendations to avoid the use of corticosteroids in the management of moderate to severe traumatic brain injury, leading to improved outcomes for patients worldwide (12). Trials of this magnitude are often required to inform clinicians of the optimal mode of therapy for critically ill patients, but they are very costly to run.

It has been estimated that a clinical trial of a similar magnitude to the CRASH trial might cost more than $400 million to run (1). In spite of costs of this magnitude, clinical trials programs can lead to important improvements in population health. In a study that examined all phase III randomised clinical trials funded by the United States National Institute of Neurological Disorders and Stroke before January 1, 2000, 28 trials with a total cost of $335 million were evaluated (13). As a result of the research program, it was estimated that the program was responsible for an additional 470,000 quality-adjusted life years, and a projected net benefit to society of $15.2 billion at 10 years (13). Clearly, while expensive, clinical trials of this nature are associated with significant societal benefits. This is important, given the increasing costs of modern healthcare and in particular the increasing cost of providing critical care services.

7.1.2 The expense of healthcare and the expense of critical care

Modern healthcare is expensive. The Australian Institute of Health and Welfare estimates that expenditure on health in Australia was approximately $121,400,000,000, in 2009-2010, or approximately 9.4% of gross domestic product (GDP). This had increased from $72,200,000,000 in 1999-2000 or approximately 7.9% of GDP (14). A large part of the increase in spending came from increased spending on services delivered in public hospitals (14).

The provision of critical care services, which are largely delivered in public hospitals in the Australian healthcare system, is a significant source of healthcare expenditure. There are data available from the United States regarding the evolving costs of providing critical care services in a modern healthcare system (15). In a retrospective observational study utilising the Hospital Cost Report Information System, a

database of hospital costs in the United States, it was reported that there was an increase in overall critical care medicine costs by 44.2% from 2000 to 2005, and an increase in the cost per day of 30.4%. The authors also reported that critical care consumed 0.66% of GDP in the United States in 2005, up from 0.56% of GDP in 2000 (15). In another retrospective cohort study utilising data from the Medicare Inpatient Prospective Payment System in the United States from 1994 through to 2004, it was reported that there was a 31.0% increase in the number of hospitalisations which involved an ICU admission from 1994 through until 2004, with an increase in the total cost from $23.77 Billion US, to $32.25 Billion US, an increase of 35.7% over the same time frame (16). The authors concluded that the rise in Intensive Care use was leading to large increases in costs for the Medicare program in the United States.

Providing critical care services in Australia is also very expensive. It is possible to draw inferences regarding the contribution of critical care to the cost of providing healthcare services in Australia from data collected by the Department of Health and Ageing for the National Hospital Cost Data Collection. In 2001-2002, 16 of the 20 highest cost Diagnosis Related Groups (DRGs), were conditions that require admission to a critical care area, including the management of premature neonates, patients undergoing heart transplantation, patients with severe burns, management of patients receiving extracorporeal membrane oxygenation, the management of patients with a tracheostomy or receiving prolonged mechanical ventilation, and those following severe trauma (17). The rankings in terms of most expensive, the estimate of the cost of caring for patients in these DRGs and the number of patients with each condition, for the years 2004-2005 through to 2008-2009 are shown in Table 7-1. These data demonstrate that patients who require treatment in a critical

care area are among the most expensive patients in the Australian healthcare system. This is reinforced when the cost per separation and the number of separations are combined. In this case the management of patients with a tracheostomy or receiving prolonged mechanical ventilation (DRG A06Z), is consistently the most expensive category in recent years (18-22). The total cost of providing critical care services was also noted to increase from $255,000,000 in 2004-2005, to $303,000,000 in 2008-2009 (22). These data provide support for the contention that the provision of critical care services is one of the most significant sources of healthcare costs in Australia.

Table 7-1. Cost, rank and number of separations for representative DRGs involving Critical Care, 2004-2005 through 2008-2009 in the Australian Healthcare System

DRG	Description	2004-2005(18)			2005-2006(19)			2006-2007(20)			2007-2008(21)			2008-2009(22)		
		Rank	**Cost***	**Seps**	**Rank**	**Cost**	**Seps**	**Rank**	**Cost**	**Seps**	**Rank**	**Cost***	**Seps**	**Rank**	**Cost***	**Seps**
A05Z	Heart Transplant	1	150	42	3	121	66	4	134	75	7	109	70	1	175	61
A40Z	ECMO	2	147	62	1	136	89	1	171	90	3	145	80	2	161	124
Y01Z	Severe Burns	3	136	121	4	121	133	2	154	109	2	146	129	5	121	158
P61Z	Neonate <750g	4	113	270	2	125	268	3	150	305	1	180	238	3	159	299
A06Z	Tracheostomy	8	80	7,953	8	84	8,281	11	91	8,408	10	92	8,468	8	98	8,904
W01Z	Severe Trauma	9	73	1,077	11	77	1,101	12	83	1,157	11	82	1,063	9	93	1,188

*DRG = Diagnosis Related Group, * Estimated national average cost per separation in $1000, Seps = Separations,*

ECMO = Extracorporeal Membrane Oxygenation

7.2 Economic Analyses and Critical Care

With the provision of critical care services being responsible for a significant proportion of healthcare costs, there is a need to evaluate the benefits that accrue from this spending. These evaluations, or economic analyses, are necessary to ensure that the limited resources available within a healthcare system are distributed in a fashion designed to maximise the benefits. There are four main types of economic analyses performed; cost-minimisation analysis, cost-benefit analysis, cost-effectiveness analysis and cost-utility analysis. In each type of study, the resources required to deliver the interventions are compared to the benefits that accrue from those interventions.

7.2.1 Cost minimisation analysis

In a cost-minimisation analysis the total cost of delivering two interventions is compared, with the outcome from the therapies assumed to be equivalent (23, 24). Thus, it would generally be preferable to choose the lower cost alternative. While cost-minimisation studies are relatively simple to perform, the conclusions that can be drawn from them are limited by the fact that they often focus on purchase or acquisition costs and do not take into account any estimate of other healthcare resources used, and that the clinical outcomes are assumed to be equivalent, when this may be difficult to establish with certainty.

An example of a cost minimisation study was reported in 2000 by Singh and colleagues (25). They reported the results of a randomised trial in intensive care patients with a pulmonary infiltrate on a chest radiograph, in which patients with a clinical pulmonary infiltrate score of ≤3 were randomised to receive either

ciprofloxacin for 3 days or standard care which was assumed to be a course of antibiotics for 10-21 days. The primary endpoints for the study were mortality, length of ICU stay, emergence of antimicrobial resistance or superinfection and antimicrobial therapy cost. The resources required to deliver the therapies in this study were obtained by recording the doses and durations of antibiotics therapy in both groups and combining this with the average wholesale price of the antibiotics. There was no attempt made to measure other resources utilised that might have been influenced by the intervention. The authors reported no difference in the mortality of patients in the two experimental groups, but there was a reduction in costs of treatment with the estimated mean cost of antibiotic therapy in the intervention group of $259 and the estimated mean cost of antibiotic therapy in the control group of $640. The authors conclude that the strategy of a short course of ciprofloxacin is to be recommended over standard therapy as it was associated with a reduction in costs associated with less antimicrobial use without adversely affecting length of stay or mortality (25).

A further example of a cost-minimisation analysis was performed and reported by Dasta and colleagues (26). This analysis compared the costs of dexmedetomidine and midazolam for long-term sedation in the ICU. The authors used data from a previous randomised trial comparing these two agents (27), that had found no difference in the primary outcome of the study, time at target sedation levels, and also no statistically significant difference in ICU length of stay, to support the assumption of similar outcomes for the two sedation regimens. For the cost-minimisation analysis the authors collected data on 84 separate items to estimate resource utilisation and added cost values to each of these from sources such as previously published studies, current procedural technology codes, and the bureau of

labour statistics. The authors concluded that the use of dexmedetomidine was associated with a cost saving of US$9,679 (95% Confidence interval $2,314 to $17,045).

7.2.2 Cost-benefit analysis

In a cost-benefit analysis both the resources required to deliver the therapies and the benefits that accrue from those therapies are expressed in monetary units (23, 24). This facilitates comparison of the costs and benefits as the two are expressed in tangible values, and allows comparison between disparate treatments (28). There are difficulties performing this type of analysis, including those related to placing a monetary value on health outcomes (23), and the difficulty in obtaining a value for the societal benefits that may accrue from a new intervention (24). As in a cost-minimisation study, the resources needed to deliver the new intervention are measured, and then unit costs are added.

There are few examples of cost-benefit analyses in the critical care literature as these studies are mostly used as a research tool (24). One example of a cost-benefit study was reported by Mendeloff and colleagues (29). They report the results of an analysis comparing the costs and benefits of procuring organ donors. The authors obtained data from published reports to estimate the resources that patients with end-stage renal failure, heart failure, respiratory failure and liver failure would require with and without transplantation, and then estimated the resources used in the process of organ procurement via charges from the organ procurement organisations. They conclude that over a range of assumptions that there would be a net benefit to society if up to US$1,086,000 was spent procuring additional organ

donors due to the reduction in healthcare expenditure post transplant and the improvements in quality of life of survivors.

7.2.3 Cost-effectiveness analysis

A cost-.effectiveness analysis involves measuring the resources involved in the delivery of a therapy and comparing these to the benefits, as measured in naturally occurring health units, such as life years gained or cases of ventilator associated pneumonia prevented (23, 24). As for other types of economic analysis, there are limitations to the interpretation of the results of a cost-effectiveness analysis. Importantly, except in the rare circumstances that a new therapy is shown to be both more effective and to use less resources, a cost-effectiveness analysis can only provide information regarding the comparative marginal cost of introducing a new therapy, it cannot address issues of opportunity cost, that is, whether the additional cost per life year saved for this therapy is more worthwhile than the benefits that may accrue from other interventions (30). Cost-effectiveness analyses are the most common type of economic analysis performed in critical care (31).

There are a number of cost-effectiveness studies published in the critical care literature (32). One example of a cost-effectiveness analysis performed in conjunction with a clinical trial in critical care was published by Angus and colleagues (33). They analysed the cost-effectiveness of a novel treatment for patients with severe sepsis, activated protein C or Drotrecogin alpha activated, that was shown in an initial randomised clinical trial (the PROWESS study) to be associated with a 6.1% absolute reduction in the risk of mortality (34). In parallel with the clinical trial, data were collected to measure the resources utilised in the patients receiving activated protein C and those receiving standard care. To assess resource utilisation, hospital

billing records of the patients enrolled in the trial were examined, to assess all resources used within the hospital, and an estimate of the resources used post-discharge was generated depending upon the hospital discharge destination for each patient. A standard conversion factor was used to convert the billing charges to actual costs. Using the results of the PROWESS study (34) to estimate the short-term survival advantage, Angus and colleagues reported that activated protein C treatment cost $160,000 per life saved at 28 days, with an 84.7% probability that the cost per life saved ratio was less than $250,000. It is interesting to note that subsequent clinical trials have not confirmed the efficacy of this treatment, and thus rendered the results of the economic analysis moot (35, 36).

7.2.4 Cost-utility analysis

The fourth type of economic analysis is a cost-utility analysis. In this type of analysis the resources required to deliver a therapy are compared to a composite measure that includes not only the increased duration of survival, but also the quality-of-life experienced by the survivors. This is particularly important in studies in critical care as the quality of life in survivors of critical illness is often measurably impaired (37). Cost-utility analysis is the recommended approach for assessing the relative costs and health benefits of new therapies in critical care (23). As the outcome measure from a cost-utility analysis is a common unit, generally quality adjusted life years (QALYs) they allow comparison of disparate interventions. Even so, there are limitations associated with cost-utility analyses. These particularly relate to the difficulties in measuring quality-of-life and variability in the methods used to perform these studies that makes comparisons of interventions difficult (38).

One example of a cost-utility analysis in critical care was performed in conjunction with the PACMAN study (39). The PACMAN study was a multi-centre randomised controlled trial to evaluate the clinical effectiveness of the use of pulmonary artery catheters in the management of critically ill patients (40). The cost utility analysis was performed alongside the clinical trial. Resource utilisation was measured by collecting data on ICU and hospital length of stay and by analysing routine data collected by the National Health Service. The researchers used a top-down method, whereby costs incurred by the whole ICU were estimated, then were divided to derive an average for a day in the ICU, which could then be attributed to individual patients depending on their length of ICU stay (39). The study found that withdrawal of pulmonary artery catheters from routine use would be associated with an estimated increase in QALYs from 3.8 to 4.0, and this increase in QALYs was associated with an estimated increased cost of £2,892. Thus the researchers concluded that for a small incremental cost, the avoidance of the use of an invasive monitoring device would be associated with an increase in the quality of life of surviving patients.

As can be seen from the above, there are a number of different approaches that can be used to perform economic analyses to ascertain the relative value of new therapies. In order to perform any of these analyses, it is necessary to measure the resources consumed in delivering the interventions being compared. The measurement of resource utilisation related to the delivery of the interventions that are being compared in a clinical trial is a complex area of performing any economic evaluation of critical care interventions.

7.3 Measuring Resource Utilisation in Critical Care Research

One of the primary goals of intensive care is to reduce mortality and morbidity of critically ill patients, and this goal may be achieved by the judicious use of interventions designed to support patients with significant organ failure. Clinical trials in intensive care commonly compare different modes of organ support (41, 42), or therapies that are designed to alter the duration or intensity of organ support (36, 43). When considering the measurement of resource utilisation in clinical trials of such interventions, in order to ascertain whether one of the interventions being compared is associated with significantly less resource consumption, it is necessary to consider the full scope of the resource utilisation that might differ between the groups of trial participants (23). There are direct resources required to deliver the intervention, for example, the resources required to acquire the medications in a drug trial, along with the resources required to deliver the medication; the disposables and the nursing time required to prepare and administer the medication. It is also necessary to consider potential differences in overall resource utilisation that may accrue as a result of the intervention under consideration. For example if a new therapy was able to reduce the number of patients who required mechanical ventilation, or reduced the duration of mechanical ventilation, it is possible that this difference could contribute to a reduction in the overall resources used by the patients who received this intervention (44). All resources that are directly or indirectly consumed by the trial participants need to be accounted for in order to estimate any potential differences in resources used.

There are a number of methods of estimating the resources utilised by participants in a clinical trial. There are bottom up or microcosting methods, where attempts are made to collect data on all individual items consumed by the trial participants in the trial. There are methods referred to as top-down approaches, where the resources consumed to run the entire ICU are calculated, and then apportioned to the individuals according to their length of stay in the ICU. On occasions, a combination of these methods is utilised. There are other methods for estimating resource utilisation, such as patient charges, and surrogate measures have been commonly used such as ICU length of stay, or workload instruments such as the TISS (6).

7.3.1 Bottom up methods of estimating resource utilisation

Bottom up methods of estimating resource utilisation, also known as ground up or micro-costing methods, involve the identification and collection of all resources used as part of the treatment regimen. In studies that utilise bottom up methods to estimate resource utilisation, each resource used in the treatment of the trial participants is recorded separately in a case report form. The goal of this method of estimating resource utilisation is to capture all the resources that make up the most significant potential differences in resource use between the two therapies that are being compared in a clinical trial (45). The major problem with attempting to measure all the resources required to deliver an intervention in a clinical trial, is the cost of attempting to do this. Indeed, it has been reported that this strategy is rarely attempted as the benefits from the specificity of this approach are outweighed by the effort involved (46).

One example of a detailed bottom up costing study in the critical care literature compared the costs associated with the use of continuous renal replacement therapy

and those associated with the use of intermittent haemodialysis for patients in the ICU with acute renal failure (47). The researchers in this study measured the resources consumed by the trial participants including; supplies (all disposables including the dialyzer and setup), replacement fluids and dialysate, the continuous renal replacement machines, nursing time, laboratory tests and physician billings. The results of this costing study were later used to perform an economic evaluation of differing modalities of renal replacement therapy in critically ill patients (48).

Bottom up methods, while more seemingly accurate and therefore offering potentially a more precise estimate of resource utilisation (49), are rarely used in the setting of a clinical trial as the benefits gained in terms of precision are rarely outweighed by the effort required to obtain the data (46). In the intensive care setting, bottom up costing is thought to be too complex, expensive and time consuming to develop, validate and implement (50).

7.3.2 Top down methods of estimating resource utilisation

An alternative approach to the bottom up method for estimation of resource utilisation is called the top down approach. The top down approach divides the sum of the annual budget for a particular hospital or hospital service by the number of patient-days, to provide an estimate of the average cost per patient-day (50). The major advantage of the top-down method of estimating resource utilisation is the relative simplicity of the data collection compared to the alternate bottom-up approach (51).

The top down method of measuring resource use in a clinical trial was previously mentioned with regards to the PACMAN study (40) and the associated economic analysis (39, 52). In order to assess the resource utilisation for those patients who were and were not managed with a pulmonary artery catheter, routine National Health Service (NHS) data sources were used to obtain an estimate of the unit cost of a day in the ICU and a day on a medical or surgical ward. For each patient in the trial, the length of stay in the ICU and the length of stay in the acute hospital were recorded (52). These data were used to calculate the resource utilisation and then coupled with an estimate of costs derived from data collected from each of the participating ICUs. As noted previously, these data were used to calculate an estimate of the cost utility related to withdrawal of the pulmonary artery catheter from routine use. Of note, the estimate of the cost per QALY gained was £2,985, with the majority of bootstrap stimulations indicating that the withdrawal of pulmonary artery catheters from routine practice would be associated with an increase in QALYs and an increase in overall costs (52).

While, as noted already, the major advantage of the top down approach is the relative simplicity of the data collection, the major disadvantage of the top down approach is a lack of precision that these data provide. A top down approach to estimate resource use is the least precise method for estimating resource use (49). In a study comparing the top down method to the bottom up method, using data from 14,915 patients treated in 72 Veteran's Affairs hospitals in the United States (53), it was found that there was significant variation between the mean cost of care for inpatient and outpatient services when a top-down methods was used as compared to a bottom up method, with correlation between the two methods as low as 0.29 in some cases.

7.3.3 Patient charges

Another method of recording the resources consumed by patients during their treatment is to use the charges reported by patient billing records that are generated by hospitals. These data are often readily available, particularly in health systems without a universal health insurance system, such as the United States, and as such are an attractive source of data for researchers. The data are derived from physician fees, drug charges, as well as accounting for the resources required to deliver the therapies to patients (49). While utilising data related to patient charges has some superficial appeal in terms of its use as a measure of resource utilisation, there is significant debate as to the validity of this method.

The seminal study to assess the relationship between patient charges and actual resource utilisation was reported by Shwartz and colleagues (54). The researchers in this study collected cost data from seven hospitals using a sophisticated hospital cost accounting system. The quantity of each product used by each patient was determined from the patient account. The charges were then compared to the actual costs, calculated from a relative value unit (RVU) approach, where each item consumed is assigned a value that reflects is relative costliness compared to the departmental costs. The RVU method is generally considered to be reasonably accurate as methods for assessing resource utilisation (54). The authors concluded that for most diagnostic categories, the ratio of cost to charges was within 10% of the estimate of total resource use as estimated by the reference standard, the RVU method. It is based upon this study that clinical researchers have utilised a cost-to charges ratio as a measure of resource utilisation.

Cost to charge ratios have been utilised in economic evaluations in critical care. The cost effectiveness of using N-terminal pro-brain natriuretic peptide (NT-pro-BNP) to assist in the management of patients in the Emergency Department was assessed in a study by Siebert and colleagues (55). The study used data from a prospective clinical trial evaluating the utility of NT-pro-BNP in the investigation of patients presenting with dyspnoea to the Emergency Department (56) to estimate the clinical utility of NT-pro-BNP. Data related to resource use was gathered via the institutions cost accounting database, with a cost to charge ratio for echocardiography services, professional fees and hospital length of stay applied. The research team used a decision analysis method to estimate the effect of the addition of the NT-pro-BNP to routine clinical judgement. The authors concluded that NT-pro-BNP guided assessment was associated with a reduction in overall resource use (as measured by total costs) with a 9.4% reduction in total costs, and an associated reduction in the number of hospitalisations and echocardiograms performed.

While patient charges have been used as a measure of resource utilisation, most commonly using a ratio of charges to actual costs, there are concerns regarding the validity of using data regarding hospital charges to determine costs and hence resource use, in the setting of clinical research. There are concerns that charges bear little resemblance to economic costs and that the use of charges may lead researchers to draw unwarranted conclusions about the relative economic efficiency of the therapies under consideration (57). This can lead to situations as encountered when researchers attempted to assess the relative costs and hence resource use associated with various methods of performing elective coronary revascularisation; conventional angioplasty, directional atherectomy, coronary artery stenting and coronary artery bypass graft surgery (58). The authors noted that there was

considerable controversy regarding the economic cost associated with each procedure, with previous studies, which used hospital charges as the basic method of assessing resource use, suggesting that atherectomy and coronary artery stenting were associated with increased resource use. The research team performed a study whereby resource utilisation was determined for each method of performing coronary revascularisation by recording directly all resource use associated with each procedure, along with a measure of nursing workload, and other hospital services consumed. Unit costs were added to each of the resources to arrive at a total cost for each method. The results of the study showed, in contrast to the previous work, that the in-hospital costs were similar for angioplasty and for coronary atherectomy, with a slightly higher cost for coronary angioplasty, although the difference was significantly less than previously suggested. The authors concluded that charge based methods for assessing resource utilisation have inherent problems and that these limitations deserve consideration in future randomised trials comparing methods of coronary revascularisation (58).

Thus, while using patient charges may seem superficially to be an attractive method of assessing resource utilisation, it has limitations that prevent the more widespread use of this method. Of note, without detailed cost accounting systems, which are often only available in for-profit hospital systems, the data to perform these analyses is often not available. Other methods of simply and precisely determining resource utilisation have also been considered.

7.3.4 ICU length of Stay

The use of ICU length of stay as a measure of resource utilisation in clinical trials has intrinsic appeal, as it is simple, easy to collect, and readily available. The relationship between resource utilisation and ICU length of stay has been investigated in a number of studies.

One of the earliest studies to assess the relationship between ICU length of stay and resource utilisation was conducted in a multidisciplinary ICU in Kingston, Ontario (59). A sample of 67 patients were randomly selected from the 251 patients admitted to the ICU from June 1 through to September 1, 1984, and had detailed data collected from the hospital cost accounting system regarding their resource use; including use of hotel services, blood bank, diagnostic services, dialysis, nursing, all pharmacy medications, physiotherapy, clerical and supplies. Data were also collected regarding ICU length of stay, TISS score (as a measure of therapeutic intensity and hence severity of illness), as well as diagnostic category. The total per diem resource use (expressed as a per diem cost) was calculated for each diagnostic category, as well as for those deemed lower or higher acuity by virtue of their total TISS score. The authors reported that fixed costs accounted for a significant proportion of total costs regardless of the diagnostic category, and thus length of stay was a significant factor in overall ICU resource utilisation as measured by total costs.

The relationship between ICU length of stay and resource utilisation was investigated in an observational cohort study of consecutive patients admitted to a general medical-surgical ICU in Springfield, Massachusetts in the USA (60). A total of 2,749 patients who were admitted to the ICU between February 1, 1983 and January 10,

1985 were included in the cohort. Data were collected on ICU length of stay, as well as hospital length of stay, a number of indices of severity of illness, including the TISS score, and information regarding the primary diagnosis requiring ICU admission. Data on resource utilisation was calculated on a cost surrogate measure, where the ICU days were weighted more heavily than non-ICU days, and the first ICU day also received a greater weighting. This method of using length of stay to estimate resource utilisation was called the weighted hospital days method. The weighted hospital days was used to assess the economic performance of 25 ICUs in the United States, in combination with an index of severity of illness, in this case the Mortality Prediction Model (MPM). The authors were able to show that the majority of ICUs fall within one standard deviation of the mean, and concluded that the weighted hospital days was a useful measure of resource utilisation when used to compare the economic performance of ICUs.

In an 11 bed, mixed medical and surgical ICU in an urban teaching hospital in Alberta, Canada, researchers conducted a study with the goal of identifying the major cost drivers for patients in the ICU (61). The researchers collected data on demographics, and clinical information regarding the patients, as well as detailed information regarding resources used by each patient including; nursing, medical, allied health professionals such as physiotherapy, speech pathology, social work and dietitian, support staff, laboratory and diagnostic imaging, medications, equipment, and supplies. The resources consumed under each of these categories was summarised using a cost value. There were 710 patients admitted to the ICU during the one-year study period, and 690 patients were included in the analysis (twenty patients were admitted solely for acute haemodialysis and were excluded). The average (SD) ICU length of stay was 4.5 (7.6) days. The average (SD)

cost/day/patient was estimated to be $1,508 (475), this was constant across most diagnostic categories as shown in Table 7-2. The authors concluded that variance in the resource use of ICU patients, as measured by costs, was largely explained by length of stay.

Table 7-2. Daily cost and length of stay by reason for admission in a mixed medical surgical ICU in Alberta Canada (61)

Reason for Admission	N	Daily Cost/ Patient[a]	Total Cost/ Stay[a]	LOS (days)
Postoperative	158	1480 +/- 600	2793 +/- 5218	1.7 +/- 3.2
Cardiovascular	126	1486 +/- 519	8007 +/- 12508	4.8 +/- 7.8
Respiratory	105	1474 +/- 349	9734 +/- 14024	6.5 +/- 9.9
Trauma	86	1568 +/- 335	13101 +/- 16294	8.2 +/- 10.7
Miscellaneous	79	1348 +/- 482	2527 +/- 3177	1.4 +/- 1.8
Gastrointestinal	57	1561 +/- 316	8750 +/- 12839	5.6 +/- 9.0
Neurologic	43	1665 +/- 418	10878 +/- 10758	6.5 +/- 6.7
Complication of procedure	13	1432 +/- 299	4776 +/- 7792	3.1 +/- 5.3
Metabolic	11	1746 +/- 516	6090 +/- 7735	3.4 +/- 4.6
Genitourinary	9	2028 +/- 423	10477 +/- 8035	5.7 +/- 4.6
Haematologic	3	1838 +/- 221	11218 +/- 8316	6.3 +/- 4.9
Total	690	1508 +/- 475	7250 +/- 11606	4.5 +/- 7.6

Data shown as mean +/- standard deviation

N= Number of patients, ICU = Intensive Care Unit

a data are presented in Canadian 1992 Dollars

In another study, the contribution of ICU length of stay to total ICU resource utilisation was assessed. The researchers gathered data from 751 consecutive patients in two hospitals in Massachusetts in the United States (62). For each patient the ICU length of stay as well as the non-ICU hospital days were tallied. Total resource utilisation was assessed using the hospital cost accounting system that directly measured resource inputs, as well as unit specific prices. It was found that ICU length of stay accounted for approximately 85-90% of all resource utilisation, as measured by total costs. It was also found that the relationship between ICU length

of stay and resource use was non-linear, with the initial ICU days being associated with significantly greater resource use, compared to later days (62).

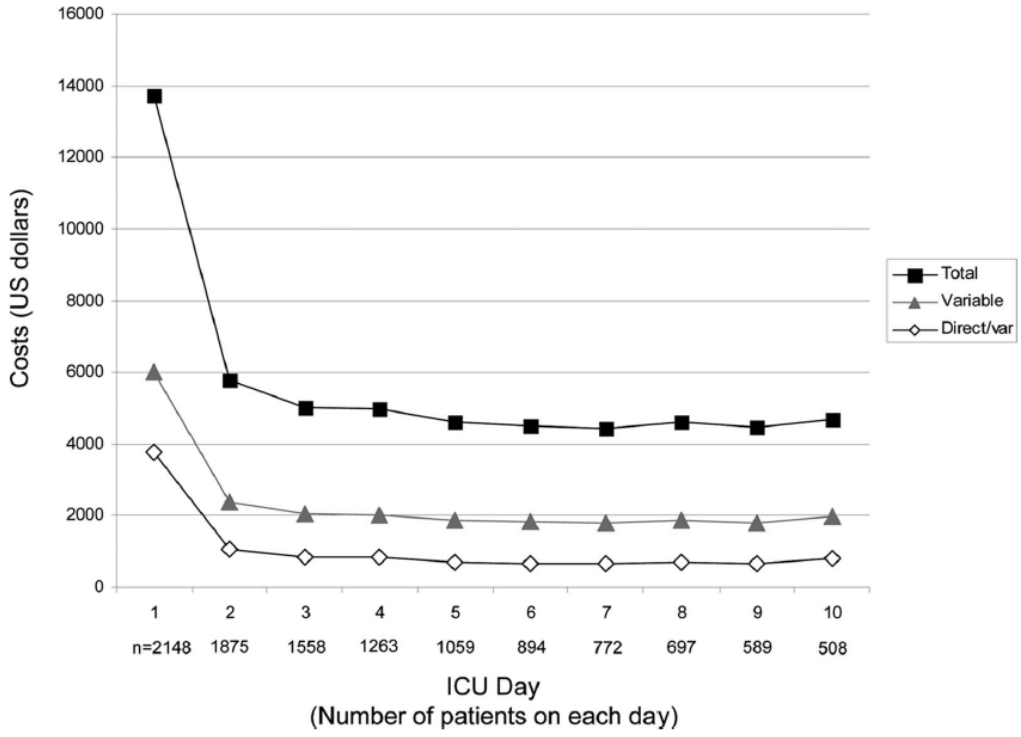
While noting that length of stay is an accepted proxy for measuring resource use and economic performance of an ICU (63), Nathanson and colleagues observed that improvements in care had led to the original model providing an overly optimistic assessment of the performance of many ICUs. As the MPM was updated to improve its precision (64), the weighted hospital days index also required revision to update it and improve the precision of the estimates that it provided. The authors used data from 135 ICUs in 98 hospitals in North America on patients admitted to the ICU between March 2001 and June 2004 to develop a new weighted hospital days model. The authors constructed a model to predict the weighted hospital days with several independent variables, the percentage of patients dying in the hospital, percentage of unscheduled surgical patients, percentage on mechanical ventilation within one hour of ICU admission and percentage discharged from the ICU to an external post-acute care facility. These variables were chosen from a set of 39 candidate variables, and an exploratory forwards and backwards stepwise approach was used to select variables for a model with the best combination of parsimony and performance. The model was attempting to predict the weighted hospital days, where ICU day one has a weight of 4, each additional day was given a weight of 2.5 and non-ICU hospital days given a weight of 1. These weights were chosen based on data from previous research (62). The authors were able to show that the Log_{10} of weighted hospital days was predicted by 4 independent variables, with an R^2 for the model of 0.47. This model was then used to show that the economic performance of ICU was better assessed using the updated model, indicating that the recalibration of the model had been necessary.

The relationship between ICU length of stay and resource utilisation was also investigated in a retrospective cohort study of 51,009 patients in the United States (44). The research team utilised data from 253 hospitals in the United States that contributed data to the NDCHealth Hospital Patient Level Database, a private information technology database serving for-profit hospitals in the United States. Resource utilisation was estimated by using total costs, captured by measuring hospital specific cost-to-charge ratios and expressed as costs. Regression analysis was used to analyse the relationship between ICU length of stay and total costs, accounting for ICU day, as well as patient demographics, hospital characteristics, patient category and mechanical ventilation status. The authors found a significant relationship between ICU length of stay and resource utilisation as measured by total costs, with an increase in the resource use on the first day, similar to previous studies (62). It is interesting to note that while the authors found a significant association between length of stay and total resource utilisation, in the model that adjusted for patient details, insurance details, hospital characteristics and ICU day, the R^2 value was only 0.276, indicating that only approximately 28% of the variability in resource use (as measured by total costs) was explained by the model.

While many authors have noted the relationship between ICU length of stay and resource consumption, not all studies have advocated the use of ICU length of stay as an accurate and precise measure of resource utilisation. In a study conducted using data from a single hospital, the Hospital of the University of Pennsylvania, Kahn and colleagues assessed the relationship between resource utilisation, again measured as total costs, and ICU length of stay (65). The researchers used the

hospital cost accounting system to gather information regarding resource use, with total costs as the unit measurement for resources consumed. All resource use was categorised each day into a variable component, a direct component, as well as specific components related to blood bank laboratory, pharmacy, radiology and respiratory therapy. The authors chose to use mean costs in their analysis, even though the mean costs were not normally distributed. The results of the study were that resource use as measured by total costs were greatest on ICU day one and fell considerably thereafter, as shown in Figure 7-1. The direct variable costs were only a small portion of the overall costs, which indicated that reductions in length of stay were not likely to result in major decrements in resource use, and thus ICU length stay measured in isolation was not necessarily a precise measure of resource utilisation.

Figure 7-1. Mean ICU Cost by ICU day. Mean total costs, variable costs, and direct variable costs by day for each ICU admission (65)



ICU = Intensive Care Unit, US = United States

Length of stay in the ICU has been used as a measure of resource consumption in clinical research. Angus and colleagues conducted a study to ascertain whether insurance status (managed care versus traditional commercial insurance and Medicare) was associated with differences in resource consumption as measured by differences in ICU length of stay (66). The study was conducted using data from the Massachusetts state hospital discharge database. Data from a total of 88,050 patients were included in the study. The primary outcome was resource consumption, as measured by the mean ICU length of stay. The authors concluded that patients covered in managed care arrangements consumed fewer resources, and that this appeared primarily due to differences in patient-related factors (such as age, severity of illness, comorbidity and reason for ICU admission) rather than other factors related to the type of insurance coverage.

In a study to assess the potential costs and consequences of implementation of Early Goal-Directed Therapy (EGDT), Huang and colleagues used ICU length of stay as the primary measure of resource utilisation (67). The researchers used estimates of ICU length of stay from the original trial of EGDT (43), as well as local data from the University of Pittsburgh Medical Centre to estimate the resource utilisation associated with various methods of implementing EGDT. The total cost was calculated by multiplying by the length of stay by a daily cost weight. The study found that as long as EGDT reduced length of stay to the degree found in the original study, that EGDT could be associated with favourable lifetime cost-effectiveness.

An analysis of healthcare utilisation associated with the use of intensive insulin therapy also used ICU length of stay as a major determinant of resource utilisation (68). This study used data from a large randomised controlled trial of intensive insulin therapy that demonstrated a reduction in mortality from 8.0% to 4.6% associated with the use of tight glycaemic control or intensive insulin therapy (69). The authors performed a post hoc analysis of data from the trial. Healthcare resource utilisation was determined largely based on length of stay, as well as the use of some other specific resources (haemodialysis, mechanical ventilation, insulin and insulin delivery systems, and blood glucose monitoring supplies). Unit costs were added to each of these resources, with ICU days forming the most significant healthcare cost. The researchers found that there was a reduction in the mean ICU length of stay of 2 days, this translated to a reduction in the median cost per patient of approximately €2,638, of which €2,007 was due to the reduction in ICU length of stay. The authors concluded, based upon the data available to that point in time that intensive insulin therapy was associated with a substantial reduction in overall medical costs (68). It should be noted that subsequent research has refuted the primary assertion that intensive insulin therapy is associated with improvements in outcomes in critically ill patients (70).

As can be seen from the above discussion, ICU length of stay has been considered a good candidate as a measure of resource utilisation for clinical research. There are problems however with using length of stay as a sole measure of resource utilisation for this purpose, including the lack of precision, and the need for a weighting to account for the different level of activity that occurs on different ICU days, with the majority activity and hence resource utilisation occurring on the first ICU day (62, 65). The report from the Second American Thoracic Society Workshop on Outcomes

Research on understanding costs and cost effectiveness in critical care (23), notes that the use of a length of stay measure may be a useful surrogate for resource utilisation, while acknowledging that its use for this purpose would require a more nuanced weighting to achieve this goal. Another means of taking into account of the varying level of activity and hence resource use that occurs throughout a patient's stay in the ICU, is the use of a nursing workload score, such as the TISS score. The TISS score is the most common workload instrument used to measure resource utilisation in the ICU (71), and as such warrants closer examination as a potential candidate as a means to estimate resource utilisation in clinical research in critical care.

7.3.5 The Therapeutic Intervention Scoring System

The TISS was developed by Cullen and colleagues in 1974 to allow quantitative comparison of patient care and research experiences of different ICUs (5). It was developed by a committee of experienced ICU physicians and nurses who assigned point values to 57 interventions commonly delivered in intensive care according to the time and effort required for nursing care. To obtain the TISS score, an experienced observer then summates the weighted interventions from the previous 24 hours to provide an overall daily score. The components of the original TISS are shown in Table 7-3. The original description of TISS described three uses for the score; utilization of intensive care unit facilities, classification of intensive care patients in the recovery room acute care unit, and cost analysis.

Utilization of Intensive Care Unit Facilities

The TISS score was used to evaluate resource utilization of the ICU facilities in the Massachusetts General Hospital to determine the level of care provided for patients regardless of their location. Seven different ICUs were surveyed as well as five general wards; a medical, paediatric, gynaecological, private surgical and a mixed ward. The wards were surveyed for approximately 850 patient days. The results of this analysis indicated that the patients in the ICU scored significantly higher TISS points than those patients managed in the general wards.

Classification of Intensive Care Patients in the Recovery Room-Acute Care Unit

Patients in the recovery room were also classified according to their severity of illness using a pre-existing scale:

Class I - post-surgical patients admitted to the routine recovery room expected to return to the normal surgical ward;

Class II - Patients requiring prophylactic observation overnight;

Class III - Patients physiologically stable but requiring intensive nursing and monitoring, frequently of an invasive nature and;

Class IV - Unstable patients requiring frequent nursing and physician care, with one or more organ failures with an unstable and unpredictable prognosis.

The TISS once again performed well in discriminating between these four categories of patients, with 30 class I patients receiving a mean (Standard Error) TISS of 5 (0.2), 30 class II patients 11 (0.7), 30 class III patients 23 (1) and 123 class IV patients 43 (1).

Table 7-3. Components of the Original Therapeutic Intervention Scoring System (5)

Intervention	Points
Cardiac arrest +/- countershock within 48 hours	4
Controlled ventilation with or without PEEP	4
Controlled ventilation with intermittent or continuous muscle relaxants	4
Balloon tamponade of varices	4
Continuous arterial infusion	4
Pulmonary artery line	4
Atrial or ventricular pacing	4
Haemodialysis in unstable patient	4
Peritoneal dialysis	4
Induced hypothermia	4
Pressure-activated blood transfusion	4
G-suit	4
Measurement of cardiac output	4
Platelet transfusion	4
Intra-aortic balloon assist	4
Membrane oxygenation	4
Hyperalimentation or renal failure fluid	3
Pacemaker on standby	3
Chest tubes	3
Assisted respiration	3
Spontaneous PEEP	3
Concentrated potassium drip (>60mEq/L)	3
Nasotracheal or orotracheal intubation	3
Endotracheal suctioning (non-intubated patient)	3
Complex metabolic balance	3
Multiple ABG, bleeding and STAT studies	3
Frequent infusion of blood products	3
Multiple parenteral lines	3
Vasoactive drug infusion	3
Continued antiarrhythmia infusions	3
Cardioversion	3
Hypothermia blanket	3
Peripheral arterial line	3
Acute digitalization	3
Acute diuresis for fluid overload or cerebral oedema	3
Active treatment for metabolic alkalosis or acidosis	3
CVP (central venous pressure)	2
> 2 iv lines	2
Haemodialysis for chronic renal failure	2
Fresh tracheostomy (<48 hours)	2
Spontaneous respiration via ETT or tracheostomy	2
Tracheostomy care	2
ECG monitoring	1
Hourly vital sign observations	1
"keep open" iv route	1
Chronic anticoagulation	1
Standard intake and output	1
Frequent STAT chems	1
Intermittent iv medications	1
Multiple dressing changes	1
Complicated orthopaedic traction	1
iv antimetabolite therapy	1
Decubitus treatment	1
Urinary catheter	1
Supplemental oxygen (nasal or mask)	1
iv antibiotics	1

PEEP = Positive End Expiratory Pressure, iv = intravenous, ETT = endotracheal tube

Cost analysis

A cost analysis was also performed in the original description of TISS. A sample of forty patients, ten from each of the above clinical classifications, was assessed. Resource utilisation was collected using the TISS. Costs were collected for each of the patients, with all laboratory tests, all equipment and supplies utilised, all medications used and a proportionate share of the salaries for all personnel summated. A regression equation was generated to estimate the cost increment per TISS point. It was estimated that cost = 54 + 10 x (TISS point). The correlation coefficient was reported as 0.79, with a small standard error. Thus the authors concluded that the cost of care for an ICU patient in their study was $10/TISS point.

7.3.5.1 The TISS update 1982; TISS-76

Due to the changing nature of interventions that are delivered in the ICU, the original TISS was updated in 1983 (6). The components of the updated TISS, which was expanded to include 76 items, are shown in Table 7-4.

Table 7-4. Components of the Therapeutic Intervention Scoring System-1983 (6)

Intervention	Points
Cardiac arrest and/or countershock with past 48 hours	4
Controlled ventilation with or without PEEP	4
Controlled ventilation with intermittent or continuous muscle relaxtion	4
Balloon tamponade of varices	4
Continuous arterial infusion	4
Pulmonary artery catheter	4
Atrial and/or ventricular pacing	4
Haemodialysis in an unstable patient	4
Peritoneal dialysis	4
Induced hypothermia	4
Pressure-activated blood transfusion	4
G-suit	4
Intracranial pressure monitoring	4
Platelet transfusion	4
Intra-aortic balloon assist	4
Emergency operative procedures (within past 24 hours)	4
Lavage of GI bleeding	4
Emergency endoscopy of bronchoscopy	4
Vasoactive drug infusion (>1drug)	4
Central iv hyperalimentation (includes renal, cardiac, hepatic failure fluid)	3
Pacemaker on standby	3
Chest tubes	3
Intermittent mandatory ventilation or assisted ventilation	3
Continuous positive airway pressure	3
Concentrated K+ infusion via central catheter	3
Nasotracheal or orotracheal intubation	3
Blind intratracheal suctioning	3
Complex metabolic balance (frequent intake and output)	3
Multiple ABG, bleeding and/or STAT studies (>4/shift)	3
Frequent infusions of blood products (>5 units/24 hours)	3
Bolus iv medications (unscheduled)	3
Vasoactive drug infusion (1 drug)	3
Continuous antiarrhythmia infusions	3
Cardioversion for arrhythmia (not defibrillation)	3
Hypothermia blanket	3
Arterial line	3
Acute digitalisation –within 48 hours	3
Measurement of cardiac output by any method	3
Acute diuresis for fluid overload or cerebral oedema	3
Active treatment for metabolic acidosis	3
Active treatment for metabolic alkalosis	3
Emergency thora-, para-, or pericardio-centesis	3
Active anticoagulation (first 48 hours)	3
Phlebotomy for fluid overload	3
Coverage with more than 2 iv antibiotics	3
Treatment of seizures or metabolic encephalopathy (within 48 hours of onset)	3
Complicated orthopaedic traction	3
Central venous pressure	2
2 peripheral iv catheters	2
Haemodialysis – stable patient	2
Fresh tracheostomy (<48 hours)	2
Spontaneous respiration via endotracheal tube or tracheostomy (T-piece or trach mask)	2
GI feedings	2
Replacement of excess fluid loss	2
Parenteral chemotherapy	2
Hourly neurological vital signs	2
Multiple dressing changes	2
Pitressin infusion iv	2
ECG monitoring	1

Hourly vital signs	1
1 peripheral iv catheter	1
Chronic anticoagulation	1
Standard intake and output (q24h)	1
STAT blood tests	1
Intermittent scheduled iv medications	1
Routine dressing changes	1
Standard orthopaedic traction	1
Tracheostomy care	1
Decubitus ulcer	1
Urinary catheter	1
Supplemental oxygen (nasal or mask)	1
Antibiotics iv (2 or less)	1
Chest physiotherapy	1
Extensive irrigations, packings or debridement of wound, fistula or colostomy	1
GI decompression	1
Peripheral hyperalimentation/intralipid therapy	1

PEEP = Positive End Expiratory Pressure, iv = intravenous, K^+ = Potassium, ABG = arterial blood gas, GI = Gastrointestinal

The revised version TISS-76 (6) also added a more thorough guideline for the collection of TISS. The purpose of the guideline was to ensure the reproducibility of the TISS scores. The guideline included:

1. The data should be collected at the same time every day, preferably in the morning, by the same observer
2. A TISS item should be checked if the intervention was performed in the previous 24 hours
3. When a patient is discharged from the ICU, the discharge TISS should reflect the previous 8 hour shift
4. The total TISS points should parallel the patients' clinical condition, decreasing as the patient improved and increasing if the patient's condition worsened. If the TISS points did not appear to parallel the patient's condition it was recommended to check the score for errors (or check the patient's condition).

5. It is recommended to check for interrelated interventions to avoid inappropriate scores. The example provided if a patient has been extubated, it is not possible to receive points for controlled mechanical ventilation
6. When related interventions are applied within a single 24-hour period, only the highest scoring intervention should be counted
7. The person collecting the TISS should preferably have experience working as a critical care nurse

A comparison was undertaken between the original TISS and the updated TISS-76. One hundred patients in three separate ICUs were evaluated. There was an excellent correlation between the two scores with a regression equation, as shown in Figure 7-2.

Figure 7-2. The Correlation between the Therapeutic Intervention Scoring System 1974 and the Therapeutic Intervention Scoring System 1982 (6)

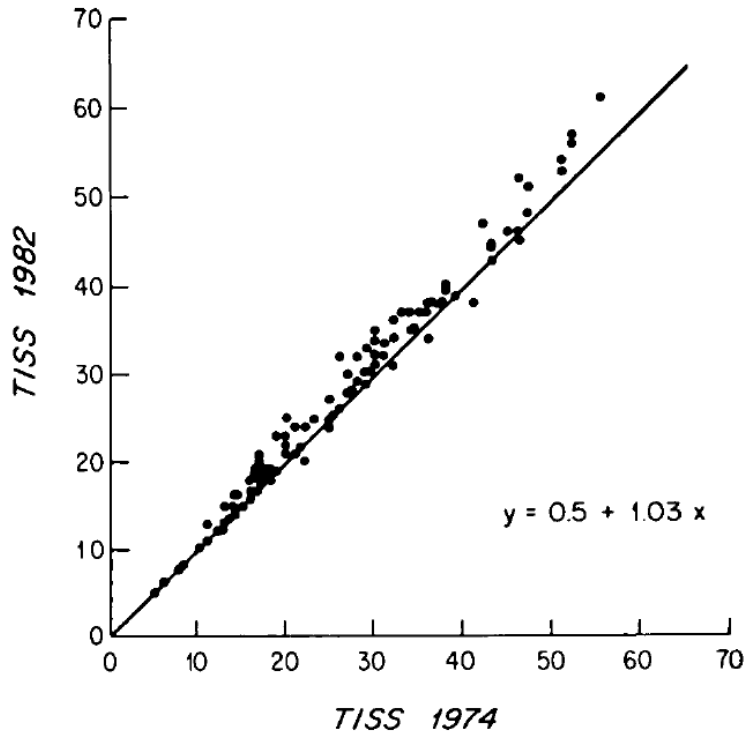


Figure 7-2 shows the results of one hundred consecutive patients in three separate Intensive Care Units who had TISS points scored according to the 1974 system and compared to the 1983 system. The regression equation was y=0.5 + 1.03x, not significantly different from the line of identity.

TISS= Therapeutic Intervention Scoring System

7.3.5.2 The revised Therapeutic Intervention Scoring System; TISS-28

With 76 items to be collected, the TISS-76 was considered by some to be cumbersome, time-consuming to collect, and some concern was raised that the items collected did not reflect all of the important activities performed in the ICU (72). The Foundation on Intensive Care Research in Europe set out to revise and simplify the TISS to address these concerns (72).

The revised TISS-28 was developed using the database of 37,000 TISS records in the Foundation for Research on Intensive Care in Europe (72). A total of 10,000 TISS records were randomly chosen from the database. The selection of items to be included in the TISS-28 was undertaken in four stages; item selection, item clustering, item reduction and cross validation.

Item Selection

The 10,000 records were divided into quartiles according to how often they were used. Items from the original TISS-76 that were seldom applied, and those that were infrequently applied and did not contribute to the discrimination between the groups were eliminated.

Item Clustering

Utilising a principal component factor analysis for all items included in the TISS-76 identified 34 factors that were responsible for 57% of the variance. This allowed some factors that were not contributing meaningfully to the TISS to be eliminated.

Item Reduction

After the first two steps, there were 34 items remaining. By merging items that described similar activities a final list of 28 items remained. The remaining items included in the TISS-28 are shown in Table 7-5.

Cross Validation

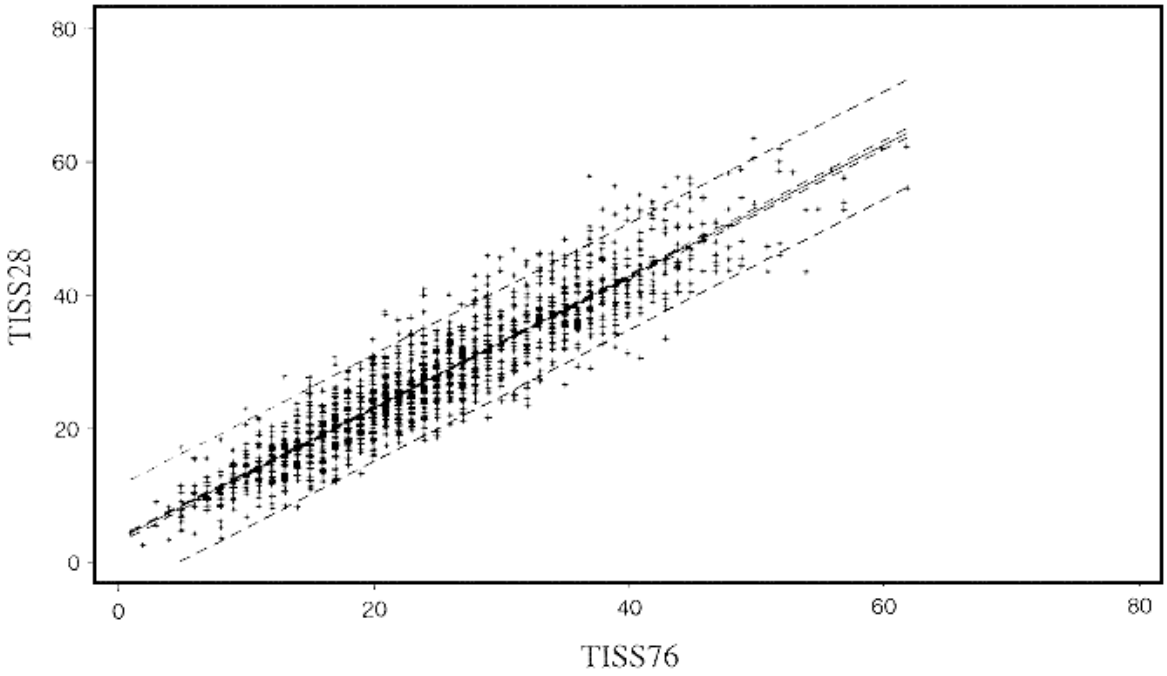
A further sample of 10,000 TISS records was randomly extracted from the database. The scores of the TISS-76 and TISS-28 were compared. The results of this analysis are shown in Figure 7-3. This showed a good correlation between the TISS-76 score and the TISS-28 score. The regression equation gave a result of TISS-28 = 3.33 + 0.97(TISS-76), with an R^2=0.86. Thus TISS-28 was able to explain 86% of the variation in TISS-76.

Table 7-5. Components of TISS-28 (72)

Component	Points
Basic activities	
Standard monitoring. Hourly vital signs, regular registration and calculation of fluid balance	5
Care of drains. All (except gastric tube)	3
Multiple iv medications. More than one drug, single shots or continuous	3
Single medication. Intravenously, intramuscularly subcutaneously and/or orally	2
Laboratory. Biochemical and microbiological investigations	1
Routine dressing changes. Care and prevention of decubitus and daily dressing change	1
Frequent dressing changes. At least one time per each nursing shift and/or extensive wound care	1
Ventilatory Support	
Mechanical ventilation. Any form of mechanical/assisted ventilation with or without PEEP, with or without muscle relaxants; spontaneous breathing with PEEP	5
Supplementary ventilatory support. Breathing spontaneously through endotracheal tube without PEEP, supplementary oxygen by any method, except if mechanical ventilation parameters apply	2
Care of artificial airway. Endotracheal tube or tracheostoma	1
Treatment for improving lung function. Thorax physiotherapy, incentive spirometry, inhalation therapy, intratracheal suctioning	1
Cardiovascular Support	
Left atrium monitoring. Pulmonary artery flotation catheter with or without cardiac output measurement	8
Peripheral artery catheter	5
Multiple vasoactive medication. More than one vasoactive drug disregard type and doses	4
Intravenous replacement of large fluid loses. Fluid administration >3L/m^2/day, disregard type of fluid administered	4
Single vasoactive medication. Any vasoactive drug	3
Cardiopulmonary resuscitation after arrest; in the past 24 hours (single precordial percussion not included	3
Central venous line	2
Renal Support	
Haemofiltration techniques. Dialytic techniques	3
Active diuresis (e.g. furosemide >0.5mg/kg/day for fluid overload	3
Quantitative urine output measurement (e.g., by urinary catheter a demeure)	2
Neurologic Support	
Measurement of intracranial pressure	4
Metabolic Support	
Treatment of complicated metabolic acidosis/alkalosis	4
Intravenous hyperalimentation	3
Enteral feeding. Through gastric tube or other gastrointestinal route (e.g., jejunostomy)	2
Specific Interventions	
Specific interventions outside the ICU. Surgery or diagnostic procedures	5
Multiple specific interventions in the ICU. More than one as described below	5
Single specific intervention in the ICU. Naso-or orotracheal intubation, introduction of pacemaker, cardioversion, endoscopy, emergency surgery within last 24 hours, gastric lavage. Routine interventions without direct consequence to the clinical condition of the patient such as radiographs, echocardiography, electrocardiogram, dressings or introduction of venous or arterial catheters, are not included	3

TISS = Therapeutic Intervention Scoring System, iv = intravenous, PEEP = Positive End Expiratory Pressure, ICU = Intensive Care Unit

Figure 7-3. Simple regression plot and 95% confidence interval of Therapeutic Intervention Scoring System (TISS)-76 items vs. TISS-28 items in 10,000 records (72)

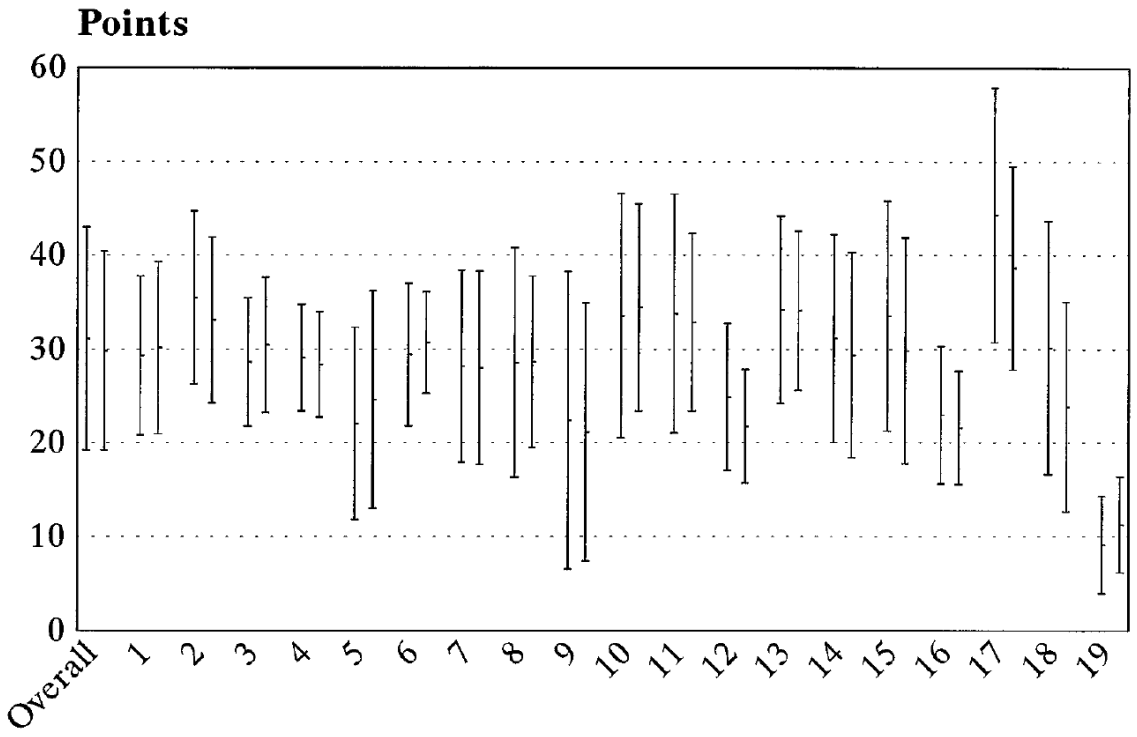


7.3.5.3 The relationship between the TISS-76 and TISS-28

The relationship between TISS-76 and TISS-28 was further evaluated in three additional studies (73-75). In the first study (74), all ICUs in Portugal (excluding the islands of Madeira and Azores) were invited to participate in a study to validate the TISS-28, with 19 out of 28 accepting the invitation. Over a three-month period from December 1994 to March 1995, all consecutively admitted patients had TISS-76 and TISS-28 recorded during the first 24 hours of their admission to the ICU. There were 1,080 patients included in the study. A 5% random sample was selected at each participating site, to check the inter-observer reliability.

The results of this study demonstrated once again, a close relationship between TISS-76 and TISS-28. The TISS scores in each of the ICUs were closely related, as shown in Figure 7-4. There was also a significant relationship between TISS-76 and TISS-28 as shown in Figure 7-5. The interobserver reliability for the TISS-28 was also good, with an intraclass correlation coefficient of 0.93 (95% CI 0.83-0.98).

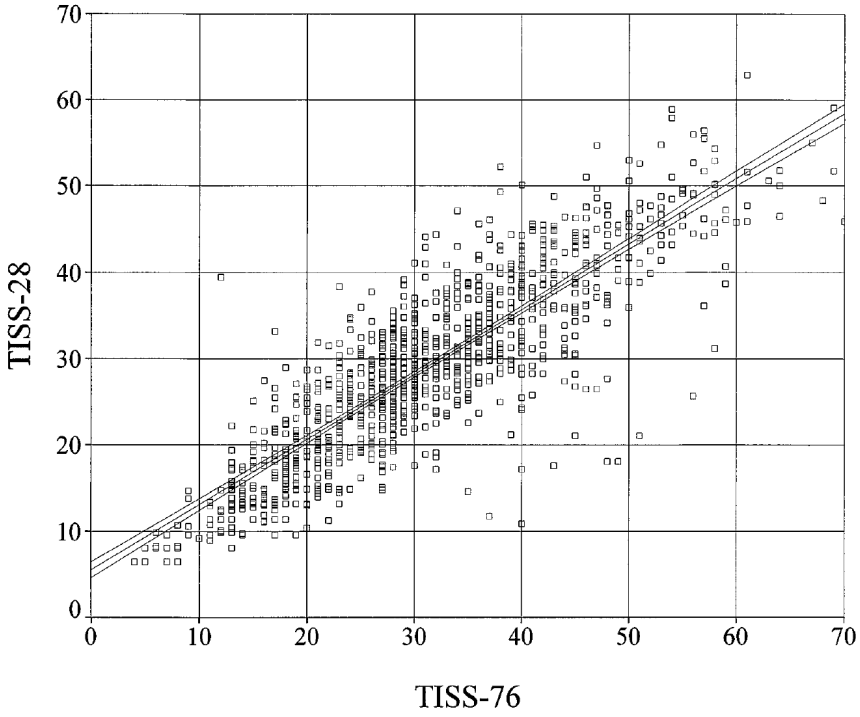
Figure 7-4. TISS-76 and TISS-28 in the overall sample and among 19 ICUs (74)



For each ICU the mean ± standard deviation for TISS-76 is indicated with the left bar and for TISS-28 right bar

TISS = Therapeutic Intervention Scoring System, ICU = Intensive Care Unit

Figure 7-5. Linear regression of TISS-76 versus TISS-28 in the 1080 patients analysed (74)



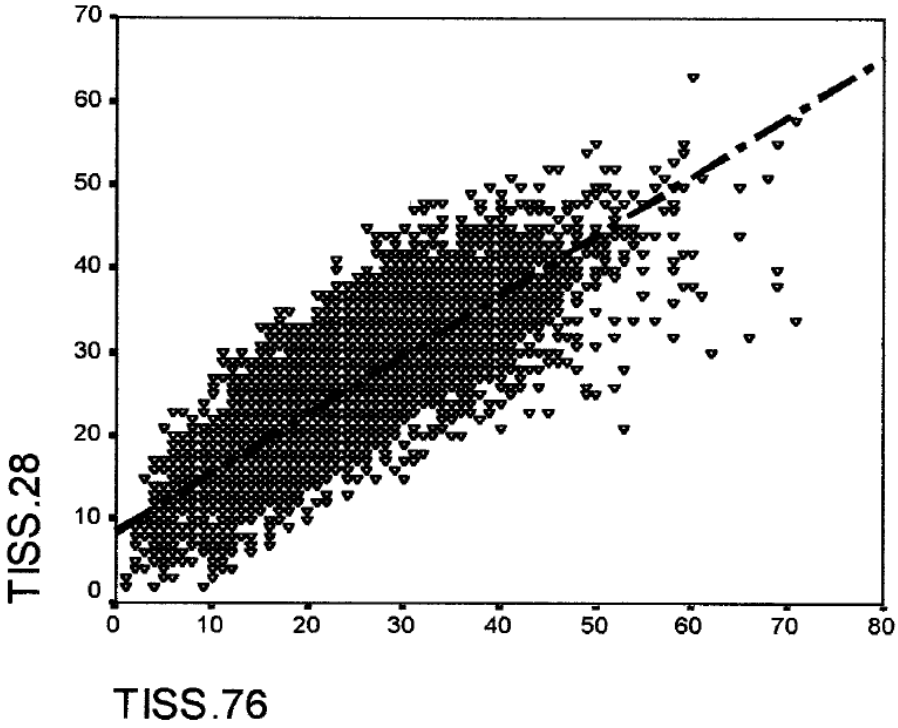
The linear regression equation established is TISS-28 = 6.217 + 0.851 x TISS-76,

$R^2 = 0.72$

TISS = Therapeutic Intervention Scoring System

The relationship between TISS-76 and TISS-28 was also examined in a study utilising the database of the Project for the Epidemiological Analysis of Critical Care Patients, a prospective multi-centre study conducted in 86 Spanish ICUs between January 1992 and July 1993 (73). A sample of 8,838 patients was collected and the TISS-76 and TISS-28 scores compared for the first 24 hours of the patients' admission to the ICU. In this study TISS-28 was found to explain 72% of the variability in TISS-76, and once again a strong correlation between TISS-28 and TISS-76 was reported, as shown in Figure 7-6.

Figure 7-6. Linear regression of TISS-76 versus TISS-28 in the 8838 patients (73)



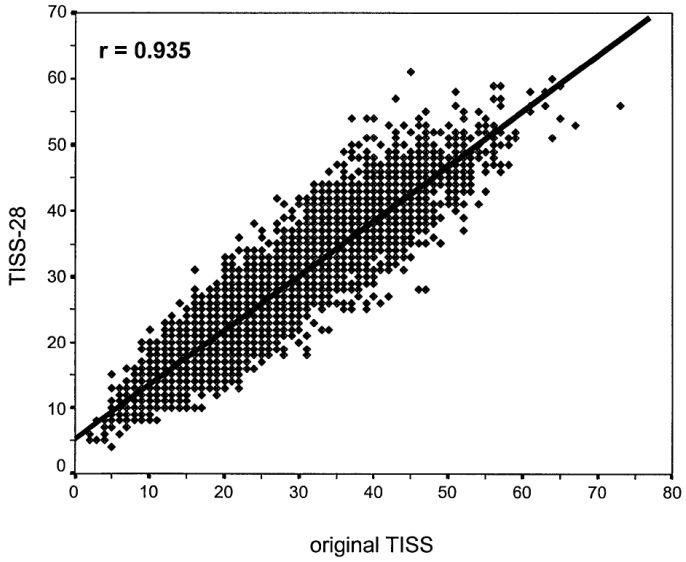
The regression equation established is TISS 28 = 8.35 + (0.712 x TISS 76),

$R^2 = 0.72$

TISS = Therapeutic Intervention Scoring System

The third study was conducted in a single ten-bed ICU in a university hospital in Cologne, Germany, that admitted surgical patients (75). The data to calculate TISS-76 and TISS-28 were retrieved from an administrative database that contained information on 1,986 admissions over a 40-month period commencing in 1993. There were a total of 10,448 patient-days with valid TISS-76 and TISS-28 scores. The TISS-28 was once again found to correlate well with the TISS-76, as shown in Figure 7-7. There was close agreement between the two scores as shown in Figure 7-8.

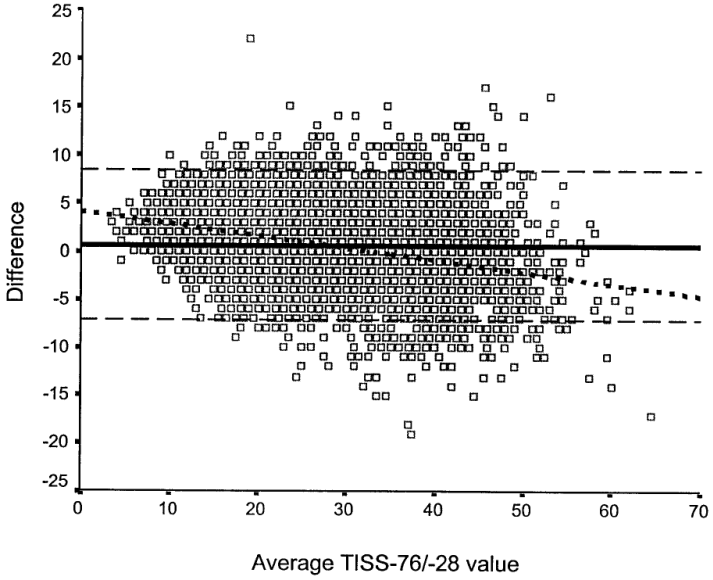
Figure 7-7. Correlation of TISS-76 and TISS-28 values based on 10,448 patient days (75)



Regression equation TISS-28 = 5.3 + 0.83 x TISS-76 (R^2 = 0.87)

TISS = Therapeutic Intervention Scoring System

Figure 7-8. Bland-Altman Plot showing the agreement between TISS-76 and TISS-28 (75)



TISS = Therapeutic Intervention Scoring System

7.3.5.4 The relationship between TISS and resource consumption

The relationship between the TISS score and resource consumption in the ICU has been examined in a number of studies.

A prospective cohort study was conducted in a general ICU in Newcastle, Australia (76). The study included 100 consecutive patients in 1983. Each patient had a daily TISS score collected, using the TISS-76 (6). The subjects were divided into four categories as per the original description of TISS (5). Resource utilisation was calculated by measuring the direct contribution of nurses' time, salaried medical staff time, consultant medical staff time, diagnostic tests performed, disposables, drugs, intravenous (IV) fluids, physiotherapy, oxygen and light and power. Consumption of maintenance and the fixed use of overheads such as building depreciation and maintenance, utilities, support services and administrative services were not included. Costs were attributed to each of the resources consumed, and then the total costs for each patient was summated.

The results of this analysis demonstrated that the total daily TISS points and average daily TISS points were greater in patients who were categorised clinically as more severely ill. The patients in the higher TISS points categories also had significantly greater resource consumption, measured in this study as higher total admission costs and average daily costs. The authors concluded that there was a strong relationship between severity of illness as measured by total TISS points and

resource consumption, as measured by total admission cost, with a correlation coefficient of 0.8894 ($p<0.001$).

A second study, was performed in a 12 bed general ICU, over a 12 week period in 1994 (77). For each patient a TISS-76 score was collected. The researchers also collected the following to measure the individual's resource consumption; the amount of nursing care delivered using a nursing dependency score, the use of disposables, drugs and iv fluids, enteral and parenteral nutrition, hired beds, haemofiltration, use of blood products, linen, physiotherapy, pathology and microbiology tests and radiology/echocardiography/neurophysiology/medical physics investigations. Each patient was also allocated a proportion of the fixed resources used by the ICU including; central hospital costs such as administration, heating, lighting and capital depreciation, medical staff salaries, ICU maintenance and hardware depreciation, ICU administration, and other ICU support staff time. Costs, divided into a variable component (the individuals resource consumption) and a fixed component (the individuals share of the fixed resources used by the ICU allocated to each patient), were attached to each of the resources, and total costs were calculated for each patient.

There were 257 patients included in the study and a total of 916 TISS-scored patient days. Of these, 205 of the patients were deemed to be true ICU patients. Regression analysis demonstrated a close correlation between daily resource consumption, measured as total daily costs and daily TISS (r=0.93). The estimate of resource utilisation, as measured in this study by total variable costs per TISS point for the patients deemed to be true ICU patients was £24.97.

A third study also examined the relationship between resource consumption and TISS scores. This study was conducted in a 12-bedded ICU in a tertiary care university hospital in Germany from between February 1998 and November 1998 (78). Both TISS-76 and TISS-28 were collected each day of ICU admission. Resource utilisation was measured for each patient using a both “top down” and “bottom up” methods. Resources used for each patient were calculated directly for items such as clinical chemistry, radiology and dialysis. High priced interventions for each patient were added separately. These were combined with a component of the nursing and medical staff salaries that was proportional to the amount of attention (as measured by the TISS score) that each patient required. In addition, non patient specific resources were allocated evenly across all patients, to account for items such as the share of total hospital resource consumption, management and administration, cleaning and other support services and the back-up salaries of the medical and nursing staff. Costs were attributed to the resources consumed according to data obtained from the hospital administration and the German regulation of charges for physicians.

There were a total of 303 patients admitted to the ICU during the study period. It was found that patient specific variables accounted for 2/3 of all resources consumed. When the resources consumed were costed, it was calculated that the patient specific cost per TISS-28 point was €36/TISS-28 point. The time taken to collect the TISS-76 was 131+/-58s compared to the 55+/-33 s to collect the TISS-28, indicating that, as would be anticipated, collecting less data required less time from the researchers.

In another study conducted in 2003, the relationship between TISS-28 points and total ICU costs was examined as part of a study to assess the resource consumption, as estimated by total costs, of ICUs in Germany (79). The study was conducted using two investigators who collected data in each of 51 ICUs randomly selected from across Germany on a single day. Data were collected on all patients, in each of the ICUs who had been admitted for greater than 24 hours. The TISS-28 was determined for the day of analysis by the study team. The resource consumption were measured in a bottom-up fashion, with drugs and consumables measured, laboratory and microbiological assays as well as diagnostic procedures measured for each patient. A top down approach was utilised to assess staffing costs, hotel costs, equipment and depreciation costs. The results of the study included an assessment that the mean cost per TISS-28 point was €32+/-13.7.

7.3.5.5 The use of TISS-28 to measure resource consumption in clinical trial

The TISS-28 score was used to estimate resource utilisation in the economic analysis of a clinical trial to evaluate the effects of inhaled nitric oxide compared to placebo for patients with acute respiratory distress syndrome (ARDS) (80). The clinical trial was conducted in 46 academic and large community hospitals in the United States between March 1996 and September 1998 (81). Patients in the ICU who were mechanically ventilated for ARDS as defined by the American-European consensus criteria (82), but with a P_aO_2/F_iO_2 ration of ≤250 rather than ≤200, were eligible for the study. Trial participants were randomised to receive either inhaled nitric oxide or placebo. The result of the trial showed that compared to placebo, inhaled nitric oxide was not associated with a reduction in the primary outcome for

the study, days alive and not receiving assisted breathing, with the participants in the inhaled nitric oxide group having a mean (SD) number of days alive and not receiving assisted breathing of 10.6 (9.8) compared to 10.7 (9.7) for those who received placebo, p=0.97. The estimate of the absolute difference was -0.1 days with 95% confidence limits -2.0 to 1.9.

The economic analysis was published separately (80). The estimate of resource utilisation in the hospital was derived using TISS-28 scores collected daily while the trial participants were in the ICU, along with hospital admission and discharge data, ICU admission and discharge data, and functional status at day 28. Hospital billing records were recorded along with centre specific cost to charge ratios. The results of the economic analysis showed that resource use, as measured by mean (SD) daily TISS-28 scores were similar in the two groups 33.5 (6.5) for the participants who received inhaled nitric oxide compared to 34.3 (6.4) for those who received placebo. The total TISS scores were also similar with a mean (SD) total TISS-28 score for those receiving inhaled nitric oxide of 560.1 (310.4) compared to 555.5 (308.7) for those receiving placebo. Based upon these data, one of the conclusions of the study was that there was no significant difference in resource utilisation in the ICU between those trial participants who were randomised to receive inhaled nitric oxide compared to those who were randomised to receive placebo.

7.4 The cost of measuring resource allocation in clinical trials

As can be seen from the above, there are numerous methods available to measure resource utilisation for the purposes of conducting clinical research. When deciding which method to employ in their research project, one of the major issues facing clinical researchers is the cost associated with collecting these data. It is clear that the attempting to measure resource utilisation in the setting of a clinical trial increases the cost of data collection (83).

The costs associated with data collection can be a significant portion of a trial budget. In a large multicentre prevention trial, it was estimated that data entry was responsible for 20% of the total trial costs and data management were responsible for a further 11% of the total trial costs (84). Having a greater number of data points also increases the complexity and costs of ensuring data quality and monitoring of data accuracy, which were also costly aspects of performing clinical trials. In another study, it was estimated that data management and audits were responsible for approximately 19.5% of trial's costs in academic medical centres performing oncology research (85). Reducing the number of data points would likely result in a reduced number of data queries, each of which can cost more than $100 each to resolve (2).

Reducing the number of data points also reduces the time taken to collect the data. It was estimated that the average time taken to collect the data for the TISS 76 was 131+/-58 seconds, and this reduced to 55+/-33 seconds when only the 28 items of the TISS 28 were collected (78). In a trial such as the NICE-SUGAR study (70), this

reduction in time taken to collect data could result in significant reductions in the cost of running the clinical trial. The NICE-SUGAR study randomised 6,104 participants, who stayed in the ICU for a median of 6 days. Assuming an hourly rate for a researcher to collect data of approximately $32 (86), it would cost approximately $39,000 just to collect data for the TISS 76, which would be halved by collecting the TISS 28, leading to a saving of approximately $19,500. This monetary saving is in excess to the time-savings of the research coordinators who could devote the additional time to more productive duties (87). Furthermore, these direct costs of collecting TISS elements do not consider the extra workload arising from data entry, data management, data queries and analysis.

A method of estimating resource utilisation that utilised less data but still produced acceptably accurate estimates of resource utilisation would be of great benefit to clinical researchers.

7.5 Aims and Hypotheses

7.5.1 Summary of the problem

Clinical trials are necessary to ensure that new therapies are effective, and it is equally important that economic analysis accompany clinical trials to ensure that new therapies are not only effective but are also cost effective. To perform an economic analysis requires the collection of data to estimate the resources consumed in the delivery of the therapies being examined in the clinical trial. This is an issue for researchers as the data necessary to accurately estimate resource utilisation in clinical trials in critical care is burdensome to collect. Of the direct approaches to the collection of data, the bottom-up methods are rarely used because of the complexity and burden of the data collection. Top-down methods lack precision and are also rarely used. Other methods of estimating resource utilisation, such as the ICU length of stay and the TISS-28 score, have been employed to reduce this burden of data collection and provide acceptable precision in estimating resource utilisation.

The simplest measure of resource utilisation in Intensive Care is ICU length of stay (78). While ICU length of stay has been advocated as a valid measure to estimate resource utilisation, its use has been questioned, particularly with regards to its precision (65). The TISS-28 score is purported to offer a significant advantage in increased precision of estimating resource utilisation in critical care (77). However, the collection of all data necessary to calculate the TISS-28 score is time consuming (78), and in the context of conducting a clinical trial, is also costly. It is currently not known whether resource utilisation in critical care could be estimated more efficiently with the collection of less data, while retaining acceptable precision.

7.5.2 Aim of the study

The aim of this study was to compare the accuracy of the estimation of resource utilisation using various methods applied to a comprehensive database of TISS scores and total ICU resource utilisation as measured by total ICU costs. The accuracy of traditional methods (ICU length of stay, TISS-28 scores) was assessed first, followed by the development and evaluation of a novel method. This novel method used multivariate regression analysis to identify a subset of the TISS-28 elements that were the strongest predictors of costs. We hypothesised this subset of TISS-28 elements would require less work to collect but may retain acceptable accuracy.

7.5.3 Primary Hypothesis

The primary hypothesis of this study was that:

Resource utilisation in critical care can be estimated with improved efficiency without altering accuracy, with the collection of only a proportion of the components of the TISS-28 score, as compared to the full TISS-28 score.

7.5.4 Secondary Hypothesis

The secondary hypothesis of this study was that:

Resource utilisation in critical care can be estimated with increased precision with the collection of only a proportion of the components of the TISS-28 score as compared to ICU length of stay.

8 Methods

8.1 Data sources

Data for this analysis were collected in the Medical ICU of the University of Aachen Hospital from March 7, 2001 until March 31, 2002. The Medical ICU is a 12-bed unit that primarily treats patients with cardiovascular disorders. Data were collected on all consecutive patients admitted to the ICU who were present in the ICU for at least 24 hours. The Hospital Research Ethics Committee of the University Hospital of Aachen gave approval for the collection of data.

8.1.1 Demographic data and clinical outcomes

Basic demographic data collected on each patient at study entry included; gender, age, admission diagnosis and severity of illness using the Simplified Acute Physiology Score (SAPS) (88). Data were also collected regarding ICU length of stay, hospital length of stay, ICU mortality and hospital mortality.

8.1.2 Calculation of TISS-28 scores

The data necessary to calculate the TISS-28 score were collected daily on all patients, as has been previously described (78, 89). Each TISS-28 component was collected for all patients on every day that they were present in the ICU. A complete list of the components included in the TISS-28 scoring system is detailed in Table 7-5. For each TISS component, a total score for that component was derived from the sum of the scores over the duration of the patient's ICU admission. A total TISS-28 score for each patient was calculated by summing all of the TISS-28 components each day to arrive at a daily TISS-28 score, and then summing these daily score over the total duration of ICU admission. A single trained investigator extracted all the

data, and a daily independent check of the data was performed to ensure data accuracy.

8.1.3 Cost data

The method for obtaining the cost data for each patient has also been previously described (78, 89). In summary the method is a combination of bottom up and top down approaches (90). Each patient was allocated non-patient specific costs and patient-specific costs.

The non-patient specific costs were allocated in a top-down fashion. The top-down approach utilises financial data at a hospital level and then allocates this down to a department level (90). These costs included an allotment of the ICUs share of central hospital costs (e.g., heating, electricity, administration, capital costs), which was allocated given the relative size of the ICU compared to the other departments within the hospital as well as ICU specific costs (e.g., administration, linen, equipment maintenance, cleaning). An amount was also allocated for the salaries of support staff and staff overhead costs (e.g., leave allowances). These non-patient specific costs were then allocated on a patient-day basis. Specifically, the total of these costs for the duration of the study was divided by the total number of patient days and allocated to each patient according to their duration of stay in the ICU.

Patient specific costs were allocated in a bottom-up fashion. The bottom up approach involves the collection of cost data at a patient level, by counting all the resources used and then transforming this into monetary units (90). For each patient, data were collected on major interventions (e.g., coronary angiography, intra-aortic balloon counterpulsation, surgical interventions), common ICU interventions (e.g., insertion of

central lines, arterial lines, bronchoscopy), medications used, fluids used, radiological procedures and other diagnostic services utilised. In addition, there was an allocation of the nursing and physician costs. The total cost of the nursing and medical staff on duty each day was calculated. This cost was divided amongst the patients present in the unit on that day, with this value weighted in accordance to workload required to care for each patient, as reflected by the patient's contribution to the ICU's total TISS-28 points accrued on that day.

Daily costs for each patient were calculated as the sum of the patient specific and non-patient specific costs. A final cost figure was arrived at by summation of the daily costs over the patients' entire ICU stay. Total costs were assumed to represent the sum total of all resources utilised by the patients for their entire ICU stay. All costs are reported in 2002 Euros.

8.2 Data analysis

8.2.1 Data description

Demographics, severity of illness data, outcome data and descriptive data regarding overall TISS-28 scores and overall ICU costs are presented as frequencies, mean and standard deviation (SD) or median and interquartile range (IQR) where appropriate. Formal assessment of the distributional properties of the continuous data was not performed. It is well known that data such as ICU length of stay and total ICU costs generally do not conform to a Normal distribution. However, it is less commonly discussed that the assumption of normality rests on the distribution of the means not of the actual data(91). It has also been empirically demonstrated that in samples of greater than 500 that linear regression remains a valid method, and in

fact performs as well or better than other methods (92). Therefore, an a-priori decision was made not to specifically assess the distributional properties of continuous variables.

8.2.2 Development of predictive models for total costs

8.2.2.1 Baseline predictive model: ICU length of stay

The simplest predictor of ICU costs is widely accepted to be ICU length of stay (62). The total duration of ICU length of stay was used as the independent variable in a univariate regression model to predict total ICU costs using a least-squares linear regression model (93). The assumptions of the model were tested using visual inspection of the residual versus fitted values plot and assessment of normal distribution of the residual values with a histogram and the Shapiro-Wilks test. Performance of the model was assessed by the R^2 value, with higher R^2 values indicating a better fit.

8.2.2.2 Baseline predictive model: Total TISS-28 score

The relationship between total TISS-28 score and ICU costs (6, 77) was also assessed using a least squares linear regression model (93). The total TISS-28 score was calculated by summation of the daily TISS-28 score for each day of admission to the ICU. The total TISS-28 score was used as the independent variable in a univariate least squares regression with total costs as the dependent variable. Once again the assumptions of the model were tested using visual inspection of the residual versus fitted values plot and assessment of normal distribution of the residual values with a histogram and the Shapiro-Wilks test. Performance of the

model was again assessed by the R^2 value with higher R^2 values indicating a better fit for the model.

8.2.2.3 Novel predictive model: Multivariate model derived from TISS-28 components and ICU length of stay

A multivariate prediction model was developed to model the relationship between ICU length of stay, the TISS-28 components and ICU costs. The initial independent variables in the model were ICU length of stay and each of the 28 individual components of the TISS-28 score whilst the dependent variable was total ICU costs.

The total score for each TISS-28 component was individually summed over the patients' entire ICU stay. As a preliminary step, the relationship between each TISS-28 component and ICU costs was assessed using univariate least-squares linear regression.

The nature of the TISS-28 components was such that significant multicollinearity in the data was anticipated (94). For example, it was expected that all ICU patients would receive standard monitoring for every day that they were present in the ICU, and it was highly likely that patients would also receive laboratory tests and hourly urine output measurements on every day in the ICU. Thus it was anticipated that certain TISS-28 components would be exact linear combinations of ICU length of stay. These relationships could lead to extreme multicollinearity in a multivariate regression model (95). Extreme multicollinearity results in unreliable predictive estimates.

To determine whether a TISS-28 component was linearly independent from ICU length of stay and thus added additional predictive value, above that of ICU length of stay, each of the TISS-28 components was added to a bivariate linear regression model containing the TISS-28 component and ICU length of stay. The TISS-28 components that added information above that offered by ICU length of stay, as evidenced by a p-value <0.20, and were present in more than 2% of the patients in the sample (96) were considered candidates for evaluation in an initial maximum multivariate linear regression model.

To assess for instability of the initial maximum multivariate model due to multicollinearity, the initial maximum multivariate model was checked using Eigenanalysis by inspection of variance inflation factors and condition index (94, 95). To ensure that the measured multicollinearity was due to real multicollinearity and not simply apparent multicollinearity, each variable was centred by subtracting the mean from the observation, and the centred variables were utilised as the predictor variables in a multivariate linear regression model (97) prior to undertaking further analysis.

To ensure that reliable estimates of the regression parameters were obtained, independent variables with the greatest variance inflation factors were sequentially removed from the model until the condition number for the regression model was <30 and no individual variable had a variance inflation factor of >15 (94). Once a stable maximum model was obtained, backwards stepwise elimination was performed (98), with variables eliminated one at a time if the p-value for regression coefficient in the

stable maximum model was >0.1. The reduced model at each step was assessed using a likelihood ratio test, with a p<0.05 indicating a significant difference between the reduced model and its immediate predecessor. When there were no further independent variables with a p>0.1 were remaining, the final remaining variables were retained in a final parsimonious predictive model.

8.2.3 Comparison of predictive models.

The R^2 value or coefficient of determination, can be interpreted as the proportionate reduction of total variation associated with the independent variables (99), or the amount of variability in the dependent variable that is explained by the combination of independent variables.

For each of the three models: the baseline model utilising ICU length of stay, the model utilising Total TISS-28 score and the novel model based on the TISS components, a 95% confidence interval around the R^2 value was constructed (100). The formula for the calculation of the 95% confidence limits for the R^2 is given as $R^2 \pm t_{(\frac{1-\alpha}{2}, n-k-1)} SE_{R^2}$ where the standard error of the R^2 value was obtained using the Olkin and Finn approximation (101) with the formula $SE_{R^2} \approx \left(\frac{4R^2(1-R^2)^2(n-k-1)^2}{(n^2-1)(3n)} \right)^{\frac{1}{2}}$. The Olkin and Finn approximation method was utilised for obtaining the standard error of the R^2 as there are no other commonly recognised methods for obtaining the standard error of the R^2 value.

Evidence that the novel model provided an estimate of total resource utilisation that was similar to the estimate of resource utilisation provided by the baseline model

using the total TISS-28 score was obtained by inspection of the 95% confidence limits of the R^2 value for the regressions. Overlap of the 95% confidence limits was taken as evidence that there was no statistically significant difference between the predictive accuracy of the models. When the 95% confidence intervals did not overlap, this was interpreted as evidence of there being a significant difference between the two models. The root mean squared error (MSE) indicating the sum of the squared residuals were also compared between models, with smaller values indicating that the model better represented the relationship between the independent variables and costs.

8.2.4 Sample size considerations

There are no strict guidelines specifying rules for calculating sample size for studies where the primary analysis will utilise multiple regression. Some authorities suggest a sample size of at least 300-400 observations, or at least 10 subject per predictor variable(102). It was deemed necessary to have a sample size of greater than 500 in order to validly use linear regression without transformation of data that was anticipated to be non-Normally distributed(92). The dataset available fulfilled all of these criteria, and the full dataset was used for the analysis.

8.2.5 Statistical software

All analysis was performed using STATA 12.1 (College Station, Tx), apart from the calculation of the 95% confidence intervals for the R^2 values(100).

9 Results

9.1 Demographic data

There were 729 patients admitted to the Medical ICU at the University of Aachen Hospital from March 7, 2001 until March 31, 2002, for whom complete data was available on all TISS-28 elements and total ICU costs. These patients formed the cohort for this study. The demographic data of the patient cohort are shown in Table 9-1.

Table 9-1. Characteristics of the patient cohort

Total patients (N)	729
Age in Years (Mean ± SD)	66 ± 14.2
Female n/N (%)	208/729 (28.5%)
SAPS II score (Mean ± SD)	31.0 ±18.2
Admission Diagnosis n/N(%)	
Acute myocardial infarction:	264/729 (36.2)
Rhythm disturbance:	79/729 (10.8)
Acute coronary syndrome:	117/729 (16.1)
Cardiac arrest:	38/729 (5.2)
Acute heart failure:	86/729 (11.8)
Pulmonary embolism:	19/729 (2.6)
Acute respiratory failure:	26/729 (3.6)
Gastrointestinal disorder:	6/729 (0.8)
Sepsis:	12/729 (1.7)
Acute renal failure:	4/729 (0.6)
Acute aortic disease:	41/729 (5.6)
Valvular heart disease:	13/729 (1.8)
Myocarditis:	8/729 (1.1)
Other*:	16/729 (2.2)
ICU discharge mortality	74/729, (10.2%)
Hospital discharge mortality n/N (%)	101/729, (13.9%)
ICU LOS (days), Median (IQR)	2 (1-4)
Hospital LOS (days), Median (IQR)	11 (5-23)
TISS-28 score Median (IQR)	40 (24-83)
Total cost of ICU stay Median (IQR)	€2177 (€1241-€3894)

SD=Standard deviation, SAPS II = Simplified Acute Physiology Score II, ICU = Intensive Care Unit, IQR = Interquartile range, LOS = Length of stay, n=number of cases,
** includes missing data*

The frequency with which the patients included in this cohort received each of the interventions included in the TISS-28 scoring system is shown in Table 9-2. All patients included in the study received both standard monitoring and laboratory testing and >99% of the patients received multiple medications, routine dressing changes, treatment for improving lung function, and urine output measurement. A single patient received intracranial pressure monitoring.

Table 9-2. Frequency of patients receiving each TISS-28 intervention

TISS Category	Frequency n/N (%)
Standard Monitoring	729/729 (100%)
Laboratory	729/729 (100%)
Single medication	11/729 (1.5%)
Multiple medications	724/729 (99.3%)
Routine dressing changes	728/729 (99.9%)
Frequent dressing changes	8/729 (1.1%)
Drains	66/729 (9.1%)
Mechanical ventilation	161/729 (22.1%)
Supplementary mechanical ventilation	562/729 (77.1%)
Care of artificial airway	127/729 (17.4%)
Treatment for improving lung function	725/729 (99.5%)
Single vasoactive medication	48/729 (6.6%)
Multiple vasoactive medication	442/729 (60.6%)
Fluid replacement	8/729 (1.1%)
Arterial line	415/729 (56.9%)
Pulmonary artery catheter	47/729 (6.5%)
Central venous catheter	242/729 (33.2%)
Cardiopulmonary resuscitation	110/729 (15.1%)
Haemofiltration	26/729 (3.6%)
Urine output measurement	727/729 (99.7%)
Active diuresis	165/729 (22.6%)
Intracranial pressure monitoring	1/729 (0.1%)
Treatment for acid-base disturbance	110/729 (15.1%)
Parenteral nutrition	185/729 (25.4%)
Enteral nutrition	146/729 (20.0%)
Single ICU intervention	90/729 (12.4%)
Multiple ICU intervention	59/729 (8.1%)
Intervention outside ICU	391/729 (53.6%)

TISS = Therapeutic Intervention Scoring System, ICU = Intensive Care Unit

9.2 Development of predictive models

9.2.1 Baseline predictive model: ICU length of stay

The relationship between ICU length of stay and total ICU costs was modelled using univariate least-squares linear regression. Intensive care unit length of stay was significantly associated with costs. There was an estimated increase of €949.65 (95% CI €912.21 to €987.08, p<0.0005) for every additional ICU day. The R^2 of 0.773 (95% CI 0.744 to 0.802) indicates that 77.3% of the variation in costs can be accounted for by variation in ICU length of stay. Details of the relationship between ICU length of stay and total ICU costs are shown in Table 9-3 and Figure 9-1.

Table 9-3. The relationship between ICU length of stay and total ICU costs.

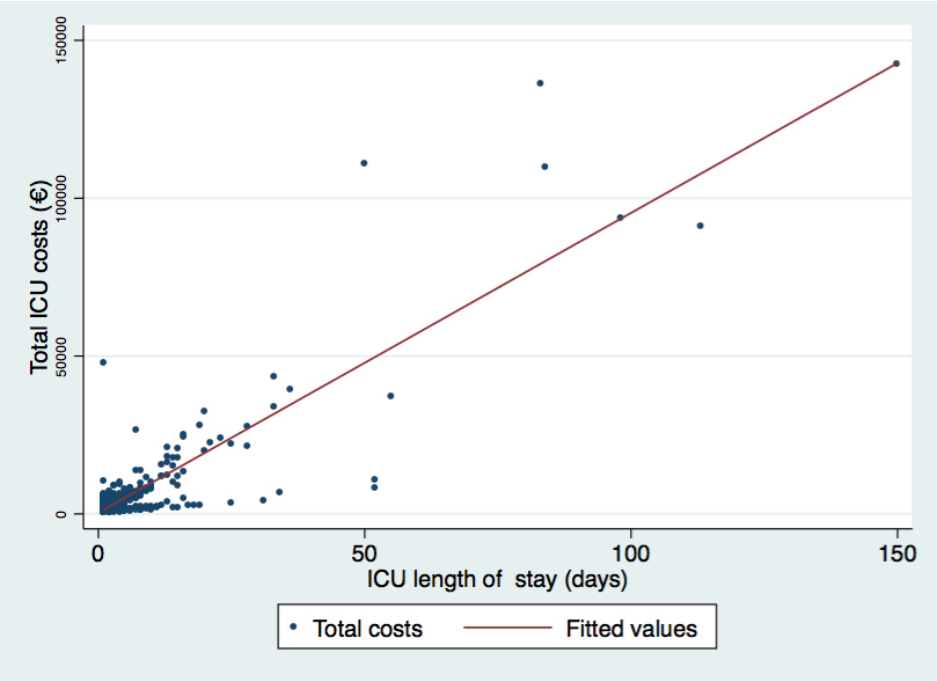
```
      Source |       SS       df       MS              Number of obs =     729
-------------+------------------------------           F(  1,   727) = 2480.50
       Model |  7.1464e+10     1  7.1464e+10           Prob > F      =  0.0000
    Residual |  2.0945e+10   727  28810242.2           R-squared     =  0.7733
-------------+------------------------------           Adj R-squared =  0.7730
       Total |  9.2409e+10   728   126935225           Root MSE      =  5367.5

------------------------------------------------------------------------------
       costs |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
     ICU LOS |   949.6488   19.06749    49.80   0.000     912.2149    987.0827
       _cons |   375.0998   214.8054     1.75   0.081    -46.61305    796.8127
------------------------------------------------------------------------------
```

ICU LOS = Intensive Care Unit length of stay

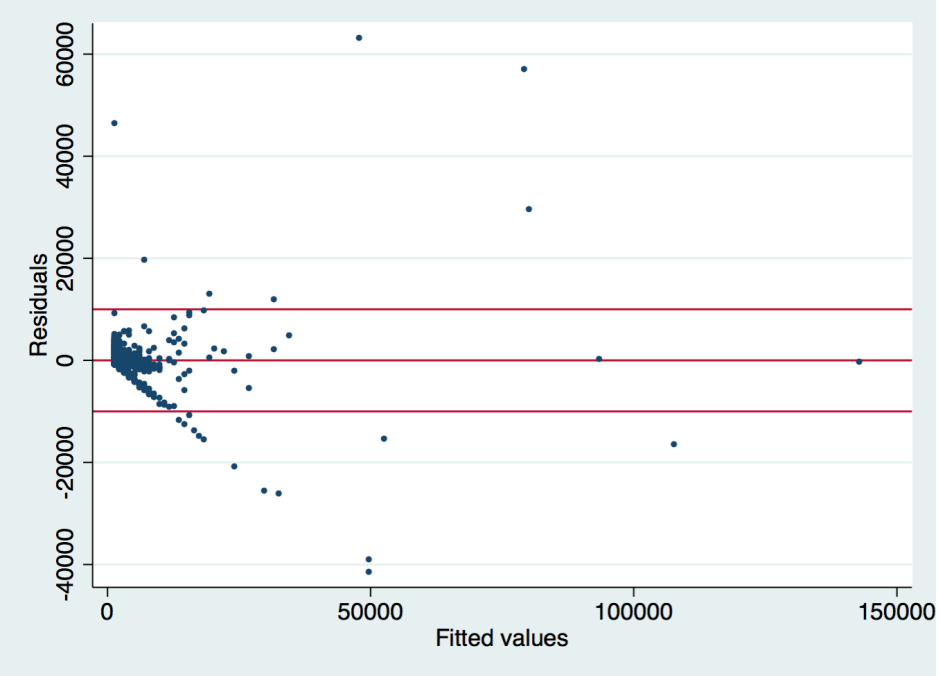
The assumptions of the model were tested. There was no significant evidence against the assumption of constant variance of the residuals, as demonstrated in the residual versus fitted values plot shown in Figure 9-2, and there was no evidence against the assumption of normal distribution of the residuals, on the Shapiro-Wilk test (z=13.46, p<0.0005), nor on the visual inspection of the histogram of the residuals, as shown in Figure 9-3.

Figure 9-1. The relationship between ICU length of stay and total costs



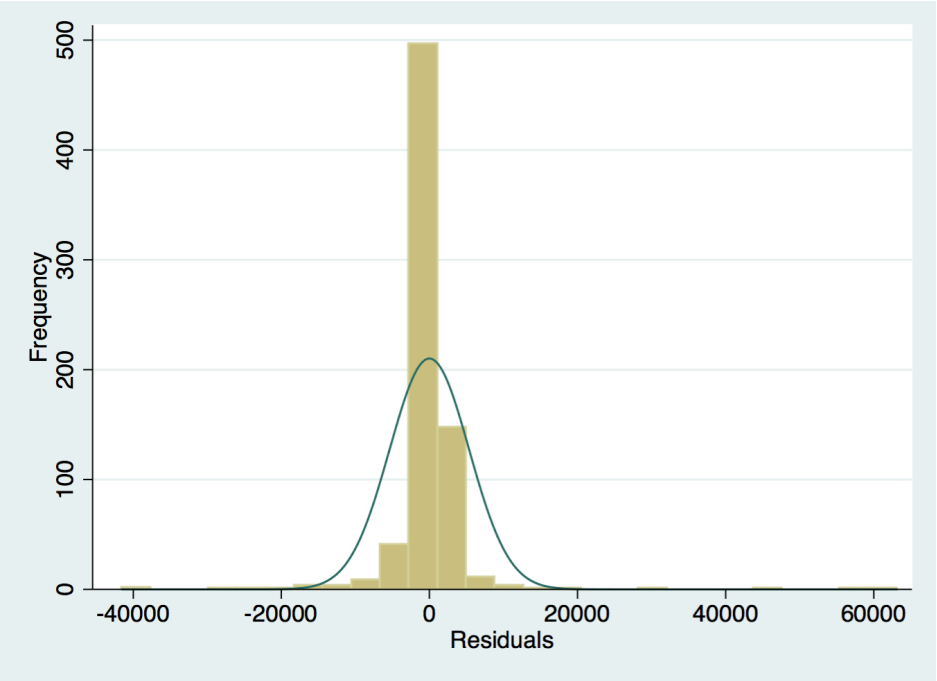
ICU = Intensive Care Unit

Figure 9-2. Residual versus fitted values plot for the regression of Total ICU costs on ICU length of stay



ICU = Intensive Care Unit

Figure 9-3. Frequency histogram showing the distribution of the residuals from the regression of total ICU costs on ICU length of stay



ICU = Intensive Care Unit

9.2.2 Baseline predictive model: total TISS-28 score

The relationship between total TISS-28 points and total ICU costs was modelled using univariate least squares linear regression. There was an estimated increase in the total costs of €33.88 per TISS point (95% confidence limits €32.76 to €35.01, $p<0.0005$). The R^2 value of 0.828 (95% confidence limits 0.805 to 0.851) indicates that 82.8% of the variability in costs can be explained using total TISS points. Details regarding the relationship between TISS-28 points and costs is shown in Table 9-4 and shown in Figure 9-4.

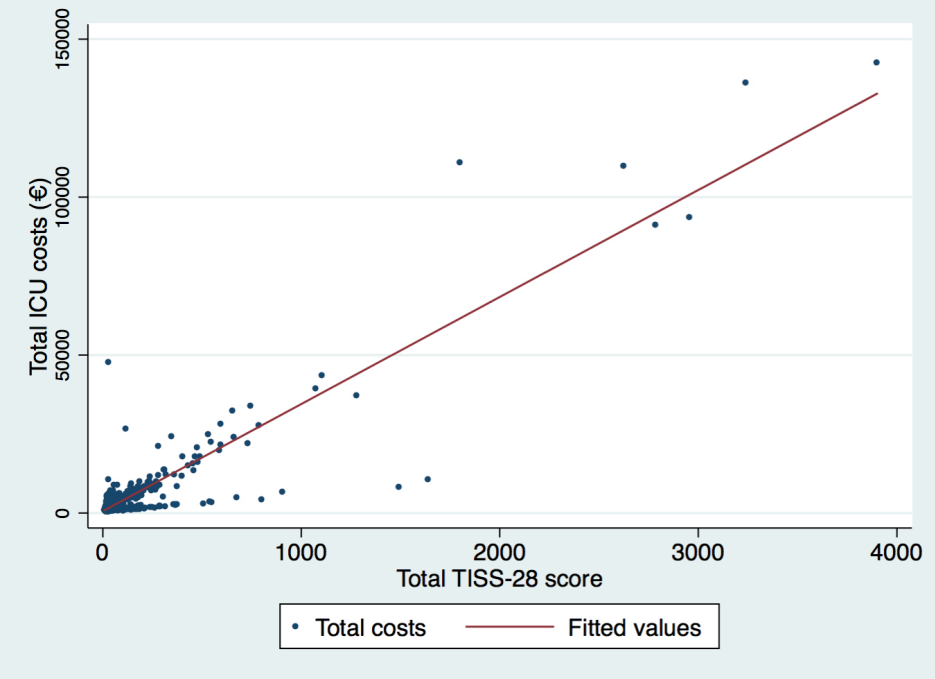
Table 9-4. Linear regression of Total ICU costs on Total TISS-28 score

```
      Source |       SS       df       MS              Number of obs =     729
-------------+------------------------------           F(  1,   727) = 3497.00
       Model |  7.6504e+10     1  7.6504e+10           Prob > F      =  0.0000
    Residual |  1.5905e+10   727    21877069           R-squared     =  0.8279
-------------+------------------------------           Adj R-squared =  0.8277
       Total |  9.2409e+10   728   126935225           Root MSE      =  4677.3

------------------------------------------------------------------------------
         costs |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
 TISS-28 score |   33.88396   .5729888    59.14   0.000     32.75905    35.00888
         _cons |   608.6356   184.8797     3.29   0.001     245.6737    971.5975
------------------------------------------------------------------------------
```

TISS = Therapeutic Intervention Scoring System, ICU = Intensive Care Unit

Figure 9-4. The relationship between TISS-28 score and Total Costs

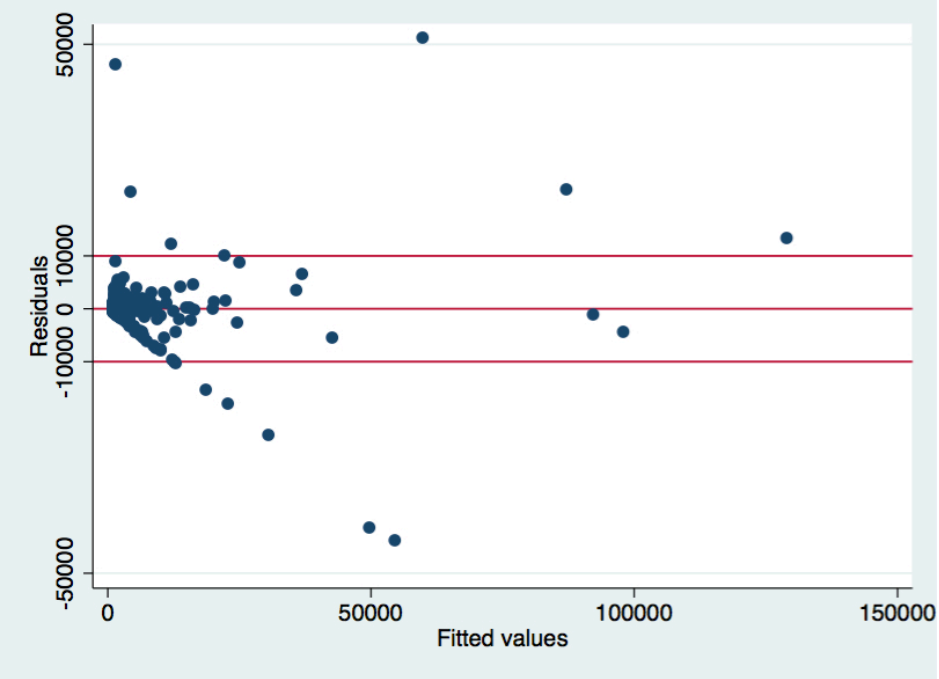


TISS = Therapeutic Intervention Scoring System

The validity of the assumptions underlying the regression model, constant variance of the residuals and normal distribution of the residuals were assessed using a residual versus fitted values plot and a histogram and the Shapiro-Wilkes test respectively. There was no significant evidence of increasing variance at increasing values of the fitted values, as shown in Figure 9-5.

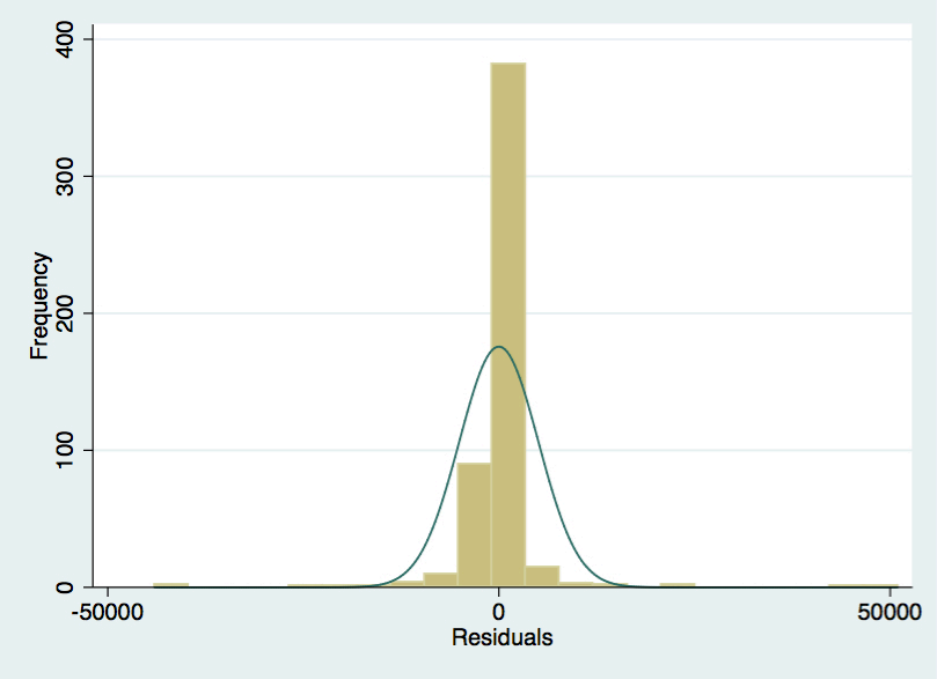
The residuals followed a normal distribution as shown in Figure 9-6 and there was no evidence to refute that the residual came from a normal distribution on the Shapiro-Wilk test (z=12.59, p<0.0005).

Figure 9-5. Residual v Fitted values plot for the regression of costs and Total TISS-28 score



TISS = Therapeutic Intervention Scoring System

Figure 9-6. Histogram of the residual values from the regression of costs and Total TISS-28 score



TISS = Therapeutic Intervention Scoring System

9.2.3 Novel predictive model: Multivariate model derived from TISS-28 components and ICU length of stay

The results of the univariate least squares regression analysis assessing the relationship between each of the 28 TISS elements and overall costs are shown in Table 9-5. There were four elements; single medication, frequent dressing changes, fluid replacement and intracranial pressure monitoring, as shown in Table 9-2, that were present in less than 2% of the patients included in this sample, and thus were not considered candidates for the multivariate analysis due to the likelihood of introducing instability in the model (96).

To determine whether a TISS-28 component was linearly independent of ICU length of stay, regression analysis including each independent variable and ICU length of stay were performed to assess their relationship with costs. The results of this analysis are shown in Table 9.6. To avoid the development of an unstable model, only variables with a coefficient $p<0.2$, were added to the initial maximum multivariate model.

The initial maximum multivariate model was then assessed for multi-collinearity. Details of the initial maximum multivariate model are shown in Table 9-7. The condition number for this initial model was 208, indicating significant multi-collinearity, and therefore an unstable model.

To assess whether this instability was due to apparent multi-collinearity rather than real multi-collinearity, each independent variable was centred (by subtracting the mean) and the initial maximum multivariate model was reassessed. Details of the initial centered maximum model are presented in Table 9-8. With the centred variables included in the model, the condition number was 189, indicating that there was real multi-collinearity and not apparent multi-collinearity.

Table 9-5. Univariate relationship between each TISS component and total costs

TISS Element	Coefficient	P	R^2
ICU length of stay (days)	949.65	<0.0005	0.77
Standard Monitoring	949.95	<0.0005	0.77
Laboratory	949.95	<0.0005	0.77
Single medication	22701.55	<0.0005	0.18
Multiple medications	1024.80	<0.0005	0.79
Routine dressing changes	954.85	<0.0005	0.77
Frequent dressing changes	4952.26	0.07	0.0045
Drains	3122.58	<0.0005	0.062
Mechanical ventilation	1445.09	<0.0005	0.78
Supplementary mechanical ventilation	1495.24	<0.0005	0.39
Care of artificial airway	1014.59	<0.0005	0.78
Treatment for improving lung function	951.47	<0.0005	0.77
Single vasoactive medication	14213.35	<0.0005	0.25
Multiple vasoactive medication	22712.18	<0.0005	0.74
Fluid replacement	3923.62	0.001	0.014
Arterial line	1257.07	<0.0005	0.75
Pulmonary artery catheter	4630.06	<0.0005	0.32
Central venous catheter	1221.24	<0.0005	0.71
Cardiopulmonary resuscitation	5731.57	<0.0005	0.08
Haemofiltration	2327.94	<0.0005	0.22
Urine output measurement	950.10	<0.0005	0.77
Active diuresis	1590.41	<0.0005	0.56
Intracranial pressure monitoring	1534.74	0.41	0.001
Treatment for acid-base disturbance	5731.57	<0.0005	0.08
Parenteral nutrition	745.24	0.002	0.01
Enteral nutrition	966.78	<0.0005	0.78
Single ICU intervention	5817.27	<0.0005	0.75
Multiple ICU intervention	12716	<0.00005	0.43
Intervention outside ICU	6733.62	<0.0005	0.23

TISS =Therapeutic Intervention Scoring System, ICU = Intensive Care Unit

Table 9-6. Regression coefficients for the regression of each TISS-28 element and ICU length of stay and costs

Independent variable	P – ICU LOS	P – independent variable	R^2
Standard Monitoring	0.50	0.62	0.773
Laboratory	0.50	0.62	0.773
Single medication	<0.0005	0.189	0.773
Multiple medications	0.001	<0.0005	0.797
Routine dressing changes	0.798	0.10	0.773
Frequent dressing changes	<0.0005	0.016	0.775
Drains	<0.0005	<0.0005	0.779
Mechanical ventilation	<0.0005	<0.0005	0.816
Supplementary mechanical ventilation	<0.0005	<0.0005	0.796
Care of artificial airway	<0.0005	<0.0005	0.795
Treatment for improving lung function	0.91	0.21	0.773
Single vasoactive medication	<0.0005	0.13	0.773
Multiple vasoactive medication	<0.0005	<0.0005	0.819
Fluid replacement	<0.0005	0.3	0.773
Arterial line	<0.0005	<0.0005	0.796
Pulmonary artery catheter	<0.0005	<0.0005	0.823
Central venous catheter	<0.0005	<0.0005	0.784
Cardiopulmonary resuscitation	<0.0005	0.85	0.773
Haemofiltration	<0.0005	<0.0005	0.814
Urine output measurement	0.039	0.42	0.773
Active diuresis	<0.0005	<0.0005	0.782
Intracranial pressure monitoring	<0.0005	0.29	0.773
Treatment for acid-base disturbance	<0.0005	0.85	0.773
Parenteral nutrition	<0.0005	<0.0005	0.784
Enteral nutrition	<0.0005	<0.0005	0.784
Single ICU intervention	<0.0005	<0.0005	0.825
Multiple ICU intervention	<0.0005	0.17	0.774
Intervention outside ICU	<0.0005	<0.0005	0.777

TISS = Therapeutic Intervention Scoring System, ICU =Intensive Care Unit, LOS =Length of stay

Table 9-7. Initial maximum multivariate model

Source	SS	df	MS	Number of obs =	729
Model	8.1469e+10	19	4.2878e+09	F(19, 709) =	277.89
Residual	1.0940e+10	709	15429820.7	Prob > F =	0.0000
				R-squared =	0.8816
				Adj R-squared =	0.8784
Total	9.2409e+10	728	126935225	Root MSE =	3928.1

costs	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]	VIF
ICU length of stay	426.9747	532.0547	0.80	0.423	-617.6165	1471.566	1453.8
Multiple iv medications	231.8042	60.05157	3.86	0.000	113.904	349.7044	147.0
Routine dressing changes	-495.5154	568.9376	-0.87	0.384	-1612.519	621.4885	1646.0
Drains	53.00179	59.68839	0.89	0.375	-64.18537	170.1889	1.2
Mechanical ventilation	-38.06778	38.70221	-0.98	0.326	-114.0524	37.91686	83.9
Supplementary ventilation	25.07317	65.34849	0.38	0.701	-103.2265	153.3729	17.8
Care of artificial airways	695.0843	109.9069	6.32	0.000	479.3023	910.8663	54.7
Single vasoactive medication	-411.9108	166.5871	-2.47	0.014	-738.9739	-84.8477	1.8
Multiple vasoactive medication	111.318	25.48551	4.37	0.000	61.28188	161.3541	8.9
Arterial line	-59.02603	20.08102	-2.94	0.003	-98.45142	-19.60065	28.7
Pulmonary artery catheter	149.9144	23.67644	6.33	0.000	103.4301	196.3987	3.2
Central venous catheter	8.04767	38.7087	0.21	0.835	-67.94971	84.04505	17.1
Haemofiltration	68.75119	35.01295	1.96	0.050	.0097216	137.4927	2.7
Active diuresis	-4.279692	24.71875	-0.17	0.863	-52.81039	44.25101	7.3
Parenteral nutrition	-92.94778	79.40702	-1.17	0.242	-248.8488	62.95325	8.0
Enteral nutrition	-174.2196	98.99415	-1.76	0.079	-368.5764	20.13713	195.4
Single ICU intervention	624.3463	75.62017	8.26	0.000	475.88	772.8125	6.8
Multiple ICU interventions	-467.2354	89.42744	-5.22	0.000	-642.8097	-291.6611	3.2
Intervention outside ICU	109.6877	47.68328	2.30	0.022	16.07039	203.3051	1.7
constant	672.8364	323.0337	2.08	0.038	38.61934	1307.053	

ICU = Intensive Care Unit, VIF = Variance Inflation Factor

Table 9-8. Centred initial maximum multi-variate model

Source	SS	df	MS	Number of obs =	729
Model	8.1469e+10	19	4.2878e+09	F(19, 709) =	277.89
Residual	1.0940e+10	709	15429820.6	Prob > F =	0.0000
				R-squared =	0.8816
				Adj R-squared =	0.8784
Total	9.2409e+10	728	126935225	Root MSE =	3928.1

costs	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]	VIF
Centred ICU length of stay	426.9761	532.0547	0.80	0.423	-617.6151	1471.567	1453.8
Centred multiple iv medications	231.8042	60.05157	3.86	0.000	113.904	349.7043	147.0
Centred routine dressing changes	-495.5167	568.9375	-0.87	0.384	-1612.521	621.4872	1646.0
Centred drains	53.00177	59.68839	0.89	0.375	-64.18538	170.1889	1.2
Centred mechanical ventilation	-38.06773	38.70221	-0.98	0.326	-114.0524	37.91692	83.9
Centred supplementary ventilation	25.07325	65.34849	0.38	0.701	-103.2265	153.373	17.8
Centred care of artifical airway	695.0841	109.9069	6.32	0.000	479.3021	910.8661	54.7
Centred single vasoactive medication	-411.9108	166.5871	-2.47	0.014	-738.9739	-84.84772	1.8
Centred multiple vasoactive medications	111.318	25.48551	4.37	0.000	61.28188	161.3541	8.9
Centred arterial line	-59.02605	20.08102	-2.94	0.003	-98.45143	-19.60066	28.7
Centred pulmonary artery catheter	149.9144	23.67644	6.33	0.000	103.4301	196.3987	3.2
Centred central venous catheter	8.04767	38.7087	0.21	0.835	-67.94971	84.04505	17.1
Centred haemofiltration	68.7512	35.01295	1.96	0.050	.0097319	137.4927	2.7
Centred active diuresis	-4.279713	24.71875	-0.17	0.863	-52.81042	44.25099	7.3
Centred parenteral nutrition	-92.94782	79.40702	-1.17	0.242	-248.8488	62.95321	8.0
Centred enteral nutrition	-174.2196	98.99416	-1.76	0.079	-368.5764	20.13715	195.4
Centred single ICU intervention	624.3463	75.62017	8.26	0.000	475.8801	772.8125	6.8
Centred multiple ICU interventions	-467.2354	89.42744	-5.22	0.000	-642.8096	-291.6611	3.2
Centred intervention outside ICU	109.6877	47.68328	2.30	0.022	16.07039	203.305	1.7
constant	4427.716	145.4845	30.43	0.000	4142.084	4713.348	

ICU = Intensive Care Unit, VIF = Variance Inflation Factor

As the centred maximum multivariate model did not reveal apparent multi-collinearity, further model development proceeded with the initial maximum multivariate model. A full stable model was developed from the initial maximum multivariate model by sequential elimination of independent variables with the highest variance inflation factor, until a stable model was obtained. The first variable eliminated was routine dressing changes with a variance inflation factor of 1646, leaving a model with a condition number of 76.7. The next variable eliminated from the model was ICU length of stay with a variance inflation factor of 280, leaving a model now with a condition number of 42.6. Following the elimination of ICU length of stay, the next variable eliminated was multiple iv medications with a variance inflation factor of 104, leaving a model with a condition number of 36.4. The next variable to be eliminated was mechanical ventilation with a variance inflation factor of 78.1, the model now had a condition number of 25.6. Enteral nutrition was the next variable eliminated from the model, with a variance inflation factor of 51.6, the model with this variable eliminated had a condition number of 16.1. The final variable eliminated in this process was arterial line with a variance inflation factor of 21.3, leaving a model with condition number of 12.4. Table 9-9 shows additional details regarding the condition indices of the eliminated variables and the condition number of the model at each step of this process.

Table 9-9 The condition index, variance inflation factors, model condition numbers and R^2 for the elimination of variables from the initial maximal multivariate model

Eliminated variable	Condition index	VIF	Model condition number after removal	R^2 after removal
Routine dressing changes	0.96	1646	76.7	0.878
ICU Length of stay	0.96	280	42.6	0.879
Multiple ivi medications	0.76	104	36.4	0.876
Mechanical ventilation	0.94	78.1	25.6	0.876
Enteral nutrition	0.95	51.6	16.1	0.876
Arterial line	0.95	21.3	12.4	0.874

VIF= Variance Inflation Factor, ICU = Intensive Care Unit, ivi = intravenous

Once the variables in Table 9-9 were removed from the initial maximal multivariate model there were 13 independent variables in the initial maximum stable model. Full details of the initial maximum stable model are presented in Table 9-10. The initial maximum stable model was used as the basis to perform backwards stepwise elimination based on individual variable predictive contributions, variables with a p>0.1 were sequentially eliminated.

The variable drains (p=0.33) was the first eliminated, with the likelihood ratio test comparing the two models returning a p = 0.33. The next variable eliminated was central venous catheter (p=0.31), with the likelihood ratio test comparing the two models returning a p=0.31. The next variable to be eliminated was parenteral nutrition (p=0.25), the likelihood ratio test comparing the reduced model gave a p=

0.24. Finally, the variable haemofiltration (p=0.11) was removed from the model, with the likelihood ratio test returning a p= 0.1. The final parsimonious predictive model is shown in Table 9-11.

Full details of the final parsimonious predictive model are presented in Table 9-11. The validity of the assumptions of the final parsimonious predictive model was assessed. There was no evidence against the assumption of constant variance of the residuals, as shown in Figure 9-7, and there was no evidence against the assumption of normal distribution of the residuals on the Shapiro-Wilk test (z=12.56, p<0.0005) nor on the histogram demonstrating the distribution of the residuals, as shown in Figure 9-8. The condition number for the final model was 8.04, with no independent variable having a variance inflation factor of >10. The R^2 value for the final parsimonious predictive model was 0.875 (95% confidence limits 0.857 to 0.891), indicating that 87.5% of the variation in total ICU costs can be accounted for by these 9 variables.

Table 9-10. Initial maximal stable model

```
      Source |       SS       df       MS              Number of obs =     729
-------------+------------------------------           F( 13,   715) =  389.13
       Model |  8.0965e+10    13  6.2281e+09           Prob > F      =  0.0000
    Residual |  1.1444e+10   715  16005013.8           R-squared     =  0.8762
-------------+------------------------------           Adj R-squared =  0.8739
       Total |  9.2409e+10   728   126935225           Root MSE      =  4000.6
```

costs	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]	VIF
Drains	58.86802	60.57357	0.97	0.331	-60.05532	177.7914	1.2
Supplenentary ventilation	135.8554	30.50749	4.45	0.000	75.9604	195.7503	3.8
care of artificial airways	597.9238	57.12667	10.47	0.000	485.7678	710.0799	14.2
Single vasoactive medication	-399.0051	164.2503	-2.43	0.015	-721.4756	-76.53457	1.7
Multiple vasoactive medication	82.80765	22.36771	3.70	0.000	38.8934	126.7219	6.6
Pulmonary artery catheter	153.3041	23.82804	6.43	0.000	106.5228	200.0854	3.2
Central venous catheter	-32.91325	29.52358	-1.11	0.265	-90.87651	25.05001	9.6
Haemofiltration	56.29124	33.65015	1.67	0.095	-9.77367	122.3562	2.4
Active diuresis	36.67228	17.64644	2.08	0.038	2.027251	71.31731	3.6
Parenteral nutrition	55.47237	40.44673	1.37	0.171	-23.93618	134.8809	2.0
Single ICU intervention	581.7925	71.91005	8.09	0.000	440.6124	722.9726	6.0
Multiple ICU interventions	-569.4637	88.42947	-6.44	0.000	-743.0762	-395.8513	3.0
intervention outside ICU	135.7903	46.8476	2.90	0.004	43.81497	227.7656	1.6
constant	1154.972	218.5602	5.28	0.000	725.8755	1584.069	

Table 9-11- Final parsimonious predictive model showing relationship between the final 9 TISS elements and total ICU costs

```
begin with full model
p = 0.3315 >= 0.1000  removing drains
p = 0.3082 >= 0.1000  removing cvc
p = 0.2457 >= 0.1000  removing pen
p = 0.1062 >= 0.1000  removing hemofiltration

      Source |       SS       df       MS              Number of obs =     729
-------------+------------------------------           F(  9,   719) =  559.90
       Model |  8.0870e+10     9  8.9856e+09           Prob > F      =  0.0000
    Residual |  1.1539e+10   719    16048472           R-squared     =  0.8751
-------------+------------------------------           Adj R-squared =  0.8736
       Total |  9.2409e+10   728   126935225           Root MSE      =  4006.1

------------------------------------------------------------------------------------------------------
                       costs |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]    VIF
-----------------------------+------------------------------------------------------------------------
      Intervention outside ICU |   140.4932    43.7495     3.21   0.001     54.60121    226.3853    1.4
     Supplementary ventilation |   145.0146   26.21754     5.53   0.000     93.54256    196.4867    2.8
    Care of artificial airways |   542.5183    42.8418    12.66   0.000     458.4083    626.6283    8.0
  Single vasoactive medication |  -440.7188   160.2008    -2.75   0.006    -755.2361   -126.2016    1.6
Multiple vasoactive medications |   89.71278   21.56653     4.16   0.000     47.37189    132.0537    6.1
     Pulmonary artery catheter |   170.1999   21.67422     7.85   0.000     127.6476    212.7522    2.6
    Multiple ICU interventions |  -617.4216   85.86729    -7.19   0.000    -786.0022    -448.841    2.8
       Single ICU intervention |   560.8517   66.91319     8.38   0.000     429.4832    692.2203    5.1
                Active diuresis |   55.66536   15.06135     3.70   0.000     26.09588    85.23484    2.6
                       Constant |   1164.256   211.5836     5.50   0.000     748.8604    1579.652
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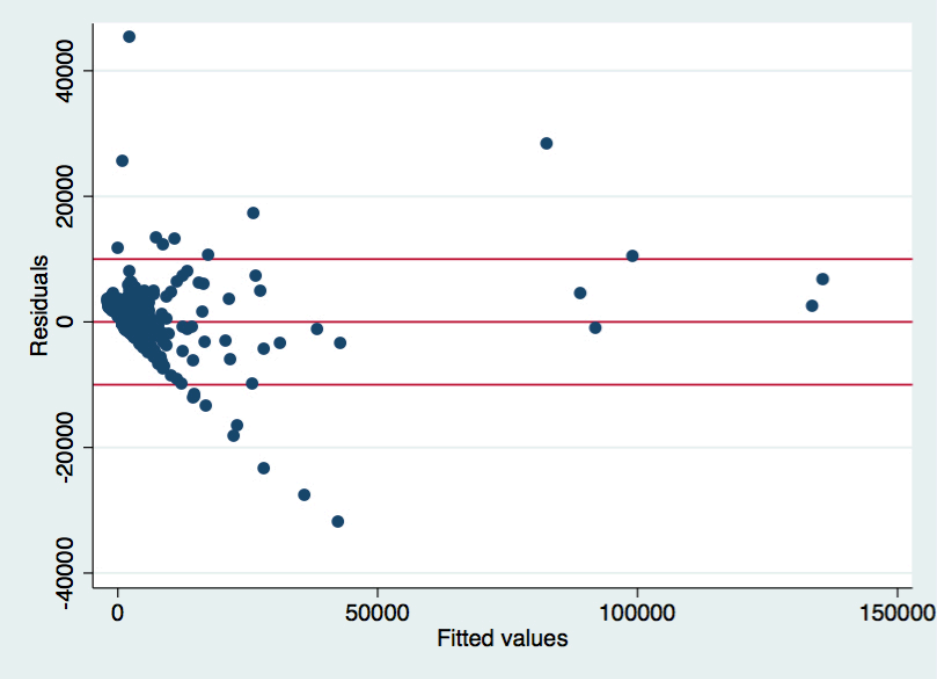
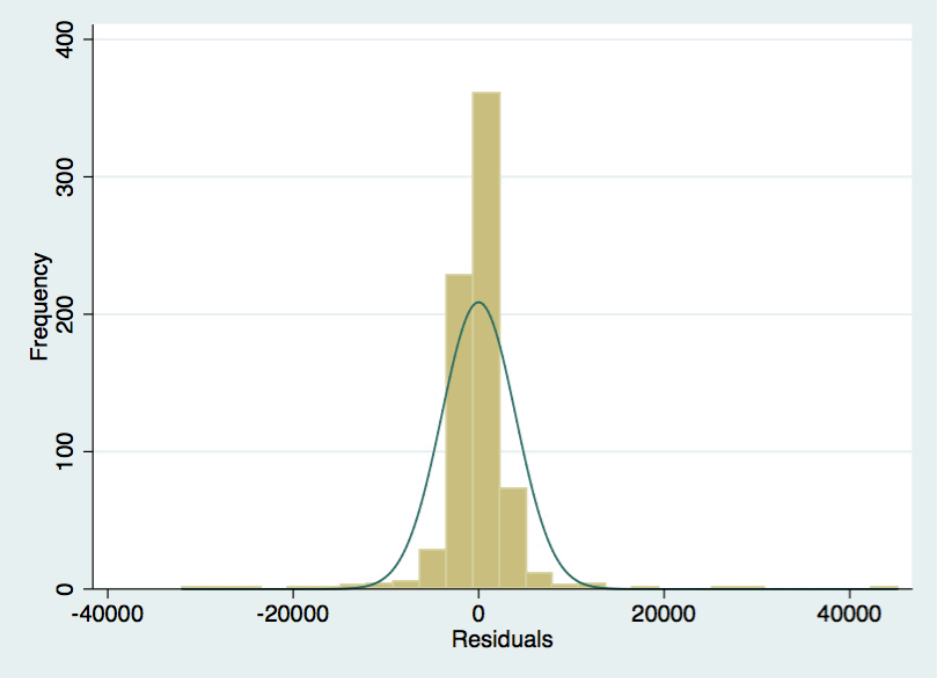
Figure 9-7. Residual versus fitted values from the regression of TISS elements and costs



TISS = Therapeutic Intervention Scoring System

Figure 9-8. Frequency histogram for the residuals from the regression of TISS elements and costs



TISS = Therapeutic Intervention Scoring System

9.2.4 Comparison of predictive models.

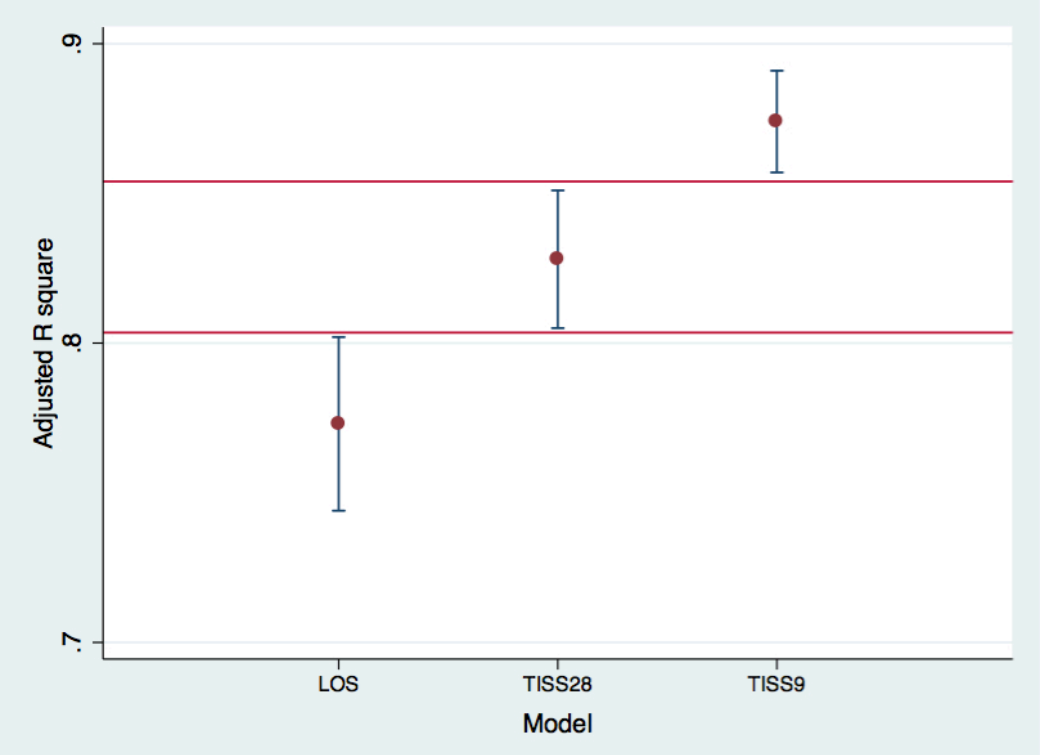
The R^2 values for the regression of baseline ICU length of stay, TISS-28 score and the final parsimonious predictive model of the 9 TISS elements, along with the 95% confidence limits is shown in Figure 9-9 and Table 9-12. The 95% confidence limits for the R^2 value for the parsimonious model, predicting costs from the 9 TISS elements, do not overlap the TISS-28 model indicating that this model better represents the resource utilisation and requires the collection of significantly fewer items.

Table 9-12. Estimates of R^2 with 95% confidence limits for the regression of costs on ICU length of stay, TISS-28 and TISS-9

Model	Estimate of R^2	Lower confidence limit	Upper confidence limit	Root MSE
ICU length of stay	0.773	0.744	0.802	5368
TISS-28	0.828	0.805	0.851	4677
TISS-9	0.875	0.857	0.891	4006

ICU = Intensive Care Unit, TISS = Therapeutic Intervention Scoring System

Figure 9-9. Comparison of the R^2 value with 95% confidence limits for the regression of costs on ICU length of stay, TISS-28 and TISS-9



ICU = Intensive Care Unit, TISS = Therapeutic Intervention Scoring System, LOS =Length of Stay

10 Discussion

The expense of modern intensive care treatments mandates that new therapies undergo rigorous evaluation prior to implementation into clinical practice, including a thorough economic analysis. The problem this raises for researchers is that performing a thorough economic analysis requires the collection of large quantities of data regarding resource utilisation, and the collection of these data is expensive and time consuming. One solution to this problem that has been previously employed has been to use surrogate markers to estimate resource utilisation. However surrogate markers such as ICU length of stay and the TISS-28 score, lack precision in the case of ICU length of stay and still require a significant burden of data collection in the case of the TISS-28 score.

The results of this analysis show that compared to the total TISS-28 score, resource utilisation can be estimated with increased precision using only a fraction of the components of the TISS-28 score. This refined TISS system, utilising only 9 data points also estimates resource utilisation with greater precision than does ICU length of stay. This offers the possibility of a more efficient and more precise method of estimating resource utilisation in clinical trials in the critical care setting.

10.1 Strengths of the current study

There are a number of strengths of this study. In particular the data utilised in this study was collected in a rigorous and robust fashion. Most importantly, the statistical methods used to analyse the data took into account the potential for collinearity to affect the regression model, an issue not previously considered in other studies in this field.

The data collected for use in this study was collected in accordance with best current research practice by well-trained investigators with rigorous methods to ensure data verification. Collection of cost data and TISS score was obtained on all consecutive patients, ensuring a representative sample of all patients treated in the ICU at this time.

The major strength to this study is the use of appropriate statistical techniques to take into account the collinearity inherent in the use of TISS-28 to estimate total costs in ICU. Collinearity occurs when two or more predictor variables are highly correlated. Collinearity is a major problem when attempting to use data such as the elements of the TISS-28 to estimate total costs as many of the variables are strongly related to each other. For example, variables in the TISS-28 such as; standard monitoring, laboratory, routine dressing changes, multiple medications, urine output measurement, treatment to improve lung function, were each performed in more than 99% of all patient days. Therefore, there was a high degree of correlation between these variables and the overall resource consumption as measured by total costs.

When significant collinearity exists, if it is not recognised and appropriately dealt with, as was done in the current analysis, it can lead to incorrect model selection, or make it impossible to determine the direction and magnitude of the effect of the predictor variables (94, 103). Previous studies (76-78, 104) had not taken into account the nature of the data that makes up the TISS-28, and thus had not accounted for the issue of collinearity. The increased precision in the prediction of resource consumption, as measured by total costs, by utilising a smaller number of predictors is almost certainly due to the careful elimination of the effect of multi-collinearity in the prediction model.

10.2 Weaknesses of the current study

There are also a number of weaknesses inherent in this study. The data was collected in a single centre, in a single country, in an ICU with a focus on cardiovascular disease. The TISS is relevant only for estimating resource utilisation in the ICU, and cannot offer information regarding resource utilisation outside the ICU. There are also potential arguments regarding the statistical methods used to analyse the data in this study, particularly the use of linear regression methods when the underlying data may not be normally distributed.

This study was conducted in a single centre, which may prompt concern regarding the generalisability of the results. Clearly the results of this study would need to be reproduced utilising data gathered in other centres to ensure the external validity of the results. It is also noteworthy that the ICU in which the data was gathered was

focussed on the management of patients with cardiovascular disorders. Thus there are vagaries to the data, for example as a cardiovascular ICU, only very few patients received a fluid bolus, many fewer than might have in a general medical or trauma ICU. The population included in this study had a low severity of illness, as evidenced by a low overall mortality rate and a relatively low SAPSS II score. It is possible that ICUs that deal primarily with trauma patients, neurosurgical patients, post-operative surgical patients or general ICUs, or those with a higher acuity would have a different profile of resource utilisation (105) and therefore the results of this study may not apply in these settings.

Another limitation to the use of TISS within the setting of a clinical trial of a new therapy in the ICU is that the TISS only records resource utilisation within the ICU. The TISS is constrained to use within the ICU, and so does not capture resources that may be utilised differentially after the ICU, or indeed once patients are discharged from hospital. Because the cost effectiveness analysis relies upon the incremental differences between the two therapies being compared, the most important data to collect are those differ significantly between the two groups and that contribute most to the differences between the two treatment arms (23). Practically this means that while all resource utilisation needs to be considered, not all is required to be measured in the same detail (23). For the majority of therapies delivered in ICU, the most significant difference in resource utilisation will occur in the ICU, and as such the use of a truncated TISS score, such as the one developed in this study, is appropriate for the purpose of estimating resource utilisation in the ICU. Indeed a number of the economic analyses evaluating the cost utility of activated protein C measured resource utilisation in greater detail within the ICU compared to

once patients had left the ICU, where a more general approach was taken (33, 106). It should be noted once again, that one of the limitations of the use of a truncated TISS to estimate resource utilisation is that it is only relevant to resources consumed within the ICU setting. If the particular therapies under consideration in a clinical trial were likely to lead to differential resource consumption for patients after discharge from the ICU, then additional methods to estimate the resources used in this setting will be required.

Another potential critique of the methods used in this analysis, relates to the use of untransformed costs as the dependent variable in the linear regression to analyse the data. It is generally taught that for linear regression it is important that the dependent variable is Normally distributed conditional upon the independent variable(s) (92, 107, 108). Cost data, such as the data used to estimate total resource consumption in this study is rarely Normally distributed, and is generally positively skewed (108). It is traditional to use a transformation of the cost data, using a logarithmic transformation to obtain a more Normal distribution (107). However transformation of the dependent variable leads to significant issues in interpreting the results of the analysis. The research question, when analysing cost data, often relates to differences in resource utilisation measured as differences in mean total costs (92, 107). With a logarithmic transformation, the results of the regression either provide information regarding a ratio of costs between the two groups or a difference in median costs if the logarithmic transformation is back transformed prior to interpretation of the results, which can be problematic (92). There is reasonable evidence that, when the sample size is large enough, generally more than 500

observations, that the Normality assumption is not mandatory for performing reliable regression analysis.

Lumley and colleagues utilised data from the Washington Basic Health Plan including 6,918 subjects (92) to assess the reliability of using linear regression of total costs on age, sex, self-rated health and Health management organisation (HMO). They used a random sampling of the data to produce 1,000 datasets each of 65, 129, 327 and 487 subjects and performed regression analysis to assess the reliability of each sample to produce the “true” mean from the total sample. They found that once sample sizes approached 500 subjects the confidence intervals of the regression coefficients contained the “true” value in >95% of cases, indicating that even for heavily skewed data, the least squares linear regression with untransformed data is sufficiently robust to produce reliable estimates of regression parameters. In this study, as the primary question related to mean costs, as a measure of resource utilisation, the simple linear regression model was chosen, above more complicated modelling approaches (108).

There are also limitations that derive from the use of a single dataset and the use of the modelling technique applied in this study. The use of a single dataset precludes the validation of the model in other settings that would be required before the current model could be recommended to be used widely. Dressing changes includes routine care for prevention of decubitus areas, which is provided to all patients in the ICU. In an ICU which primarily cares for patients with cardiac disease and where almost half of the patients were admitted with acute myocardial infarction or acute heart failure, it

is not surprising that few patients received more than 3L/m^2/day for large fluids losses. Vasoactive drugs are counted in the TISS-28 regardless of dose or type, and thus medication that do not require central access, such as hydrallazine, GTN or digoxin, may be counted in the multiple vasoactive medications.

There are some other apparent vagaries in the current model that can be explained by the data. While it may appear incongruous that both being on a single vasoactive agent and being on multiple vasoactive agents could both be included in the same model to explain resource utilisation, however as the data is collected on a daily basis, patients can be on multiple vasoactive agents early on in the course of their illness, and a single agent later in the ICU stay, with both of these time periods contributing significantly to the estimation of resource consumption. It is also notable that the item multiple ICU interventions is associated with a negative coefficient. This may be a random statistical aberration, or it may indicate that patients who require multiple ICU interventions are sicker, and therefore have a higher mortality and a shorter ICU length of stay and thus require less resource utilisation overall. These issues would need to be addressed in a validation study.

The use of a backwards stepwise procedure for variable selection has been criticised by some(109), but is recognised in standard statistical texts as valuable for producing regression equations worthy of further consideration(110). Further confirmatory studies are required and could further investigate the possibility that utilising data elements that may appear more clinically plausibly related to resource consumption

in a general ICU population, such as ICU length of stay, parenteral nutrition, mechanical ventilation, or the use of continuous renal replacement therapy.

It should also be noted that the modelling does not take into account variability that arises from system and organisational factors, such as ICU capacity. It is well recognised that factors such ICU bed availability can have a significant impact upon ICU resource use(111), and this may need to be taken into account in further confirmatory studies.

10.3 Comparison to other studies

While almost all instruments for assessing workload in the ICU have been used to assess resource utilisation, there has been a large preference for the use of TISS (71). The only alternate method for assessing resource utilisation in the ICU, specifically designed to use data regarding workload and intervention is the Omega system (112, 113).

The Omega score was developed in France in the 1980s, as a simple and reliable indicator of direct ICU costs (113). The instrument uses 47 procedures or interventions divided into three categories; procedures recorded only once during the ICU stay irrespective of their reiteration, procedures recorded every time they are performed and procedures recorded daily. The Omega score is recorded every day and the final score is a single value calculated at the end of the ICU stay.

The association between the Omega score and resource utilisation has been assessed in a number of studies. A single centre study was reported by Chaix and colleagues (112). This study, from a single hospital with a total of 108 ICU beds, was conducted in the medical ICU that comprised 26 beds and used data from 73 patients to develop a model and subsequently 29 patients to validate the model. The resource utilisation was computed from the patients' medical record, plus pharmacy, laboratory and blood bank logs. These units of resource consumption had unit costs added from the actual hospital expenditures. The authors then developed a model with mean total ICU costs as the dependent variable and the components of the Omega score Ω1, Ω2, Ω3 and total Ω, as well as variables for procedures occurring during the ICU stay, the Nine Equivalents of Nursing Manpower use score (NEMS), the Simplified Acute Physiological score (SAPS II), and length of stay. The model development process used backwards stepwise regression. The final predictive model contained only 4 variables; Ω1, Ω2, Ω3, as well as the indicator for procedures occurring during the ICU stay. The final R^2 value was 0.826, less than the R^2 for the TISS-9 as found in this study. The comparison of observed costs in the validation sample of 29 patients to the costs predicted by the Omega score was only 0.596.

In a separate study, Sznader and colleagues reported the results of study where Omega score was used to predict total ICU costs (113). In this study the Omega score was calculated from the 47 items and tallied once at the end of the ICU stay. The dependent variable was total resource consumption, as measured by total costs. The costs were the sum of the direct costs attributable to the patients' care and the indirect costs associated with the general hospital maintenance, hoteling, overheads

and depreciation. The study used data from only 121 patients admitted to one of 5 ICUs in France in 1992. The authors used mean direct costs as the dependent variable and used the Omega score as the independent variable, along with length of stay, and length of mechanical ventilation. The authors found that the Omega score was correlated with total direct costs, with a R^2 value of 0.9.

Both of these studies had sample sizes that were significantly smaller (n=73 and n=121) than the sample used in the current study (n=729). The Omega score is not widely used outside of France, while TISS is the workload instrument most widely used to estimate resource consumption (71). The Omega score still requires a large burden of data to be collected, with 47 items, significantly more than the 9 items required for the TISS-9.

Moran and colleagues have reported the results of a study designed to assess the ability of the Omega score and the TISS to predict total ICU costs. The authors measured resource utilisation by measuring medications used, procedures, pathology, radiology, physiotherapy, nursing staff (actual minutes of nursing time), medical staff, overheads and other residual resources, with unit costs attached to each. The total cost was the sum of the costs for each patient. The TISS-76 (6) used to measure the TISS score and was compared to the Omega score, with the scores for both scores totalled over the entire ICU admission. The researchers divided their data into 2 components, chosen randomly; a prediction set comprising 80% of the data and a validation set comprising the other 20%. They analysed data from survivors and non-survivors separately. The authors produced a model to predict

total ICU costs that included age, Omega score, APACHE III score and ICU length of stay, for both survivors and non-survivors, and reported that the model including the Omega score had a significant advantage compared to models that include the TISS score, with a p value <0.0001. The authors did not report the details of the model that included TISS, and did not report modelling for all patients combined, only those with survivors and non-survivors modelled separately. The authors noted that the TISS-28 may be more cost effective for routine collection and would be an appropriate candidate for a predictor variable for total costs. This study has demonstrated that collection of 9 of the TISS-28 variables is sufficient to predict resource utilisation with acceptable precision, further improving the cost-effectiveness of data collection.

As noted in the introduction, previous studies have assessed the relationship between TISS and ICU resource utilisation, generally measured as total costs. The study by Slayter and colleagues (76) used the TISS-76. Only 100 participants were included in the study. The authors assessed the relationship between total TISS points and total costs, and found a strong correlation between the two, with a correlation coefficient of 0.89. There was no assessment of the workload required to collect all 76 items of the TISS, and collinearity between items was not addressed. Dickie and colleagues also assessed the relationship between TISS and costs (77). The TISS-76 was collected in 257 patients on every day of the ICU stay, and compared to the total resource utilisation, represented as total costs. The authors reported a strong relationship between TISS and costs, with a correlation coefficient of 0.93, and an estimated increase of £24.98 per TISS point. Again the analysis did not take into account the time taken to collect data on all 76 items to assess the TISS each day. The study by Graf and colleagues (78), in assessing the relationship

between the TISS and total costs did report the difference in time to collect the data for the TISS-76 and the TISS-28, but did not assess the need to collect all 28 items in the TISS-28, nor assess the relationship between the individual items for possible collinearity. The study by Moerer and colleagues (79) is the only multi centre study to assess the relationship between TISS and resource consumption. The data was however only collected on a single day in each ICU included in the study, so that total TISS points for the patients and total costs for the patients ICU were not analysed. As such the results of this study are not directly comparable to the results of the current analysis.

10.4 Generalisabilty of the results

The result of this study, that 9 specific elements of the TISS-28 score can be utilised to provide a reasonable estimate of resource utilisation in the critical care setting, may be seen to have limited generalisability, but the methods used to derive this result may have very important implications for the measurement of resource utilisation in clinical trial in critical care.

The original TISS 28 score was developed in the United States in the 1970's(5) and was subsequently revised and revalidated in the US and in Europe(6, 72-75). While it is notable that there have been previous studies have validated the TISS-28 in a German context(78) and this data was obtained in a German ICU, there has been only a single study(104), with a relatively small sample size that have previously attempted to assess the relationship between the full TISS-28 and resource

utilisation in an Australian context, and this study is now more than 20 years old. There are marked differences between the healthcare systems in the US, Germany and Australian that could mean that the main drivers of resource utilisation might be represented by different elements of the TISS-28, or by procedures or processes not included in the TISS-28. Changes in the use of technology, including the increasing use of continuous renal replacement therapy(114) and decreasing use of monitoring devices such as the pulmonary artery catheter,(115), also mean that the TISS-28 score, which was initially developed and validated more than 20 years ago, may not be the optimal means of estimating resource utilisation in critically ill patients. One means of dealing with this limitation would be to collect data on TISS-28 elements, as well as other resource intensive interventions, as well as individual cost data within the setting of a major critical care clinical trial, either in a heterogenous population, such as included in the SAFE study(116) or the NICE-SUGAR study(117). It is also possible that the main drivers of resource utilisation would be different in specific populations, such as those with sepsis(118) or acute kidney injury(42). A concurrent investigation performed alongside studies such as these could add great value in this field of investigation.

There are always difficulties with performing health economic evaluations. Differences in health care systems, changes in demographics, technology and community expectations, make the development of tools to assess resource utilisation difficult. Current clinical practice in Intensive Care in Australia and New Zealand has changed markedly in recent years with larger numbers of lower acuity patients(119), as well as changes in monitoring and therapeutic technology. These changes mean that tools to assess resource utilisation may need regular updating

and recalibration in order to remain a valid method of assessing resource consumption.

One of the reasons for developing a new tool for measuring resource consumption, is the time and expense of collecting the large amount of data required to perform these calculations. The use of newer information systems, clinical information systems and computerised medical records, may also lead to both changes in actual resource consumption, but also change way that data to record resource utilisation is able to be collected. As these clinical information systems become more widespread the need for tools to measure resource utilisation will changes, and this may need to be taken into account in future studies.

While there is still further work required to expand the generalisability of the results of this study, it is clear that future work in this field, should recognise and take into account the fact that data of this type is very likely to have significant collinearity, and as such analysis should take this into account. The results of this study have clearly demonstrated that there by taking into account the collinearity inherent in this data, that a parsimonious tool can be developed to assist in the measurement of resource utilisation in critical care.

10.5 Further research

The results of this study demonstrate that it is possible to estimate resource utilisation with increased precision while using only a portion of the elements of the

TISS-28 score, by taking into account the collinearity inherent in the TISS-28. This result offers promise for critical care researchers as a potential tool for performing economic analysis in conjunction with clinical trials. However there remain some questions that require attention prior to the widespread adoption of this method for assessing resource utilisation.

This study collected data in a single centre, dealing with patients with primarily cardiovascular diseases. Validation of the results in other settings, in general medical and surgical ICUs, in specialty ICUs such as those that focus on neurosurgical or cardiothoracic surgical conditions is required. It has been well documented that management in specialty units such as those devoted to the care of patients with acute neurological injury is associated with improved outcomes (120), and thus the resource utilisation is likely to be different in these units. The organisation, staffing and patient populations in ICUs are also quite heterogenous internationally (121), and the patterns of resource utilisation would also likely be quite different accordingly. Consideration should be given to validating the results of this study in other countries and healthcare systems.

The components of the TISS-28 were considered important in the 1990's when the instrument was initially refined (72). Changes in critical care management practices and technology may have had an impact on nursing workload such that further refining of the components of a TISS score could lead to a more accurate estimation of resource utilisation. Pulmonary artery catheters were once commonly placed in critically ill patients, but after a number of clinical trials demonstrated no evidence

that they provided benefits to patients (40, 122-125), the use of pulmonary artery catheters has markedly decreased in recent years (115). Pulmonary artery catheters were placed in patients who were more unwell, and required more intervention, and thus used greater resources. These resource intensive patients are now managed with less invasive monitoring (126), but are still likely to require resource intensive treatments. In the current model, the presence of a pulmonary artery catheter is likely to represent a marker of the severity of illness, but an updated version of an instrument to estimate costs might need to include less invasive methods of monitoring of cardiac output to account for the increase in resources used by these critically ill patients. Similarly, new therapies have become more widely used, such as extra-corporeal membrane oxygenation (ECMO) (127, 128). These new technologies are associated with increased resource use (129), and future iterations of an instrument to estimate resource utilisation might need to take into account the use of new expensive therapies.

Before we recommend widespread use, we therefore recommend a validation study repeating our current methods, which pay close attention to the role of multi-collinearity, using a cost-database collected over multiple centres with updated TISS variables collected on each patient-day, in order to identify an efficient subset of TISS variables that most accurately predict costs. This validation might appropriately take place within the context of a large clinical trial, such as the SAFE study(116), the NICE-SUGAR study(117), the RENAL study(42) and the CHEST study(130). This validation study may also be able to collect data on other elements not included in the TISS-28, to assess the contribution of these to overall resource utilisation, and also separately assess the relationship between an efficient scoring system for

estimating resource utilisation based upon a truncated TISS-28 score and the fixed and variable components of actual resource utilisation as measured by total costs.

11 Conclusions

Clinical trials are necessary to ensure that new therapies are effective, and it is equally important that economic analyses accompany clinical trials to ensure that new therapies are not only effective but are also cost effective. To perform an economic analysis requires the collection of data to estimate the resources consumed in the delivery of the therapies being examined in the clinical trial. This can be a problem for researchers as the data necessary to accurately estimate resource utilisation in clinical trials in critical care is burdensome and expensive to collect. Existing methods for estimating resource utilisation are either too burdensome, in the case of ground up methods or micro-costing methods (46) or lack precision in the case of bottom down approaches (49). The use of patient charges has been suggested as a convenient means of estimating resource use, but again there are significant problems with the use of patient charges for this purpose (57). Intensive care length of stay has also been advocated as a measure to estimate resource utilisation, however its use has been questioned, particularly with regards to its precision (65). The use of a workload instrument such as the TISS-28 has been recommended as a tool to estimate resource utilisation in clinical trials in critical care (23), although there remain questions regarding the residual burden of data collection and the precision of the estimates of resource utilisation produced using this method.

This study has demonstrated that resource utilisation in critical care can be estimated with improved efficiency, as well as improved precision, with the collection of only 9 of the components of the full TISS-28 score. These 9 components also estimate

resource utilisation with greater precision than ICU length of stay. Researchers in critical care, who are contemplating conducting an economic analysis alongside a clinical trial should consider collecting a subset of TISS data elements to facilitate the estimation of resource utilisation.

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