Estimating Patients’ Energy Requirements: Cancer as a Case Study

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Keywords

Cancer, clinical nutrition, energy expenditure, energy requirements, dietetic practice, indirect calorimetry, metabolic rate, resting energy expenditure
Abstract

The nutritional care and management of patients includes provision of adequate nutrition support to ensure that they attain and maintain a desirable body weight, improve nutritional status and avoid negative outcomes associated with over- or underfeeding. The success of nutrition support relies on accurately estimating energy requirements so that adequate energy and nutrients can be provided to the patient. Energy requirements are most accurately determined by measurement of energy expenditure. Most methods for doing so however are expensive, time-consuming, require trained technicians to perform them and are therefore impractical in the clinical setting. As such, prediction equations, which are easy to use, inexpensive and universally available, are commonly used to estimate the energy requirements of hospitalised patients. The accuracy of these equations however is questionable. Recently, a new portable hand-held indirect calorimeter (MedGem™, HealtheTech, USA), which has been promoted for its ease of use and relatively short measurement time, has been validated in healthy subjects but is yet to be validated in patients with illnesses.

Weight loss and malnutrition occur commonly in patients with cancer and are often thought to be associated with disturbances in energy metabolism caused by the tumour. Minimising weight loss is an important goal for the nutritional care of patients with cancer. The ability to accurately determine the energy requirements of these patients is therefore essential for the provision of optimal nutrition support.

This research project proceeded in two phases. Phase 1 aimed to determine current methods used by dietitians for estimating adult patients’ energy requirements using a descriptive study. Results of this study informed phase 2, which aimed to investigate differences in energy expenditure of cancer patients compared to healthy control subjects and to compare different methods for determining energy requirements of people with cancer in the clinical setting.

To address phase 1 a national cross-sectional survey of dietitians working in acute care adult hospitals was undertaken to determine their usual dietetic practice with respect to estimating patients’ energy requirements. Responses to the survey (n=307, 66.2%) indicated a large variation in dietitians’ practice for estimating energy requirements particularly with respect to the application of methods involving injury factors. When applied to a case study, these inconsistencies resulted in an
extremely wide range for the calculated energy requirement, suggesting that there is
error inherent in the use of prediction methods, which may be associated with
negative consequences associated with under- or overfeeding. The types of patients
for whom dietitians estimate energy requirements appears to be heavily influenced
by feeding method. Initial dietetic education was identified as the main influencing
factor in the choice of method for estimation of energy requirements.

Phase 2 was addressed using four studies based on the same study population – a
case-control study, two clinical validation studies and a measurement methods
study. Patients had histologically proven solid tumours, excluding tumours of the
breast, prostate and brain, and were undergoing anti-cancer therapy (n=18). Healthy
control subjects were group matched to cancer patients by gender, age, height and
weight from a purposive sample (n=17). Resting energy expenditure (REE) was
measured by respiratory gas exchange using a traditional indirect calorimeter (VMax
229) and the MedGem indirect calorimeter. A measurement methods side-study
established that steady state defined as a three-minute period compared to a five-
minute period measured REE within clinically acceptable limits. REE was also
predicted from a range of prediction equations.

Analyses of available data found that REE in cancer patients was not significantly
different from healthy subjects, with only a 10% higher REE observed in this sample
of cancer patients when adjusted for fat free mass. For both cancer patients and
healthy subjects the portable MedGem indirect calorimeter and all prediction
equations did not measure or estimate individual REE within clinically acceptable
limits compared to the VMax 229 (limits of agreement of approximately -40% to 30%
for both the MedGem and prediction equations).

Collectively, the results of this research project have indicated that current practical
methods for determining patients’ energy requirements in a clinical setting do not
accurately predict the resting energy expenditure of individual subjects, healthy or
with cancer. Greater emphasis should therefore be placed on ensuring intake meets
requirements. For this to occur, dietetic practice should be focused on directly
monitoring both patients’ actual energy intake and patient outcomes, such as
weight, body composition and nutritional status, to determine whether energy
requirements are being met. This research has led to multiple recommendations for
dietetic practice, focusing on the standardisation of education practices.
Recommendations for future research address methodological improvements.
List of Relevant Publications

Publications included in the thesis


Reeves MM, Davies PSW, Bauer J, Battistutta D. Reducing the time period of steady state does not affect the accuracy of energy expenditure measurements by indirect calorimetry. Journal of Applied Physiology, 2004; 97:130-134.


Relevant publications not included in the thesis

Relevant Conference Presentations


Koutsoukos MM, Capra S. Use and abuse of prediction equations to estimate energy requirements: the use of a case study to illustrate professional practice. Accepted, 24th European Society of Parenteral and Enteral Nutrition Congress, Glasgow, September 2002.

Koutsoukos MM, Capra S. Predicting energy requirements in the acutely ill: the need for caution. Australian Society for Medical Research Brisbane Postgraduate Medical Research Conference, Brisbane, 2002.
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<th>Description</th>
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<tbody>
<tr>
<td>ABS</td>
<td>Australian Bureau of Statistics</td>
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<tr>
<td>ADP</td>
<td>Adenosine diphosphate</td>
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<tr>
<td>AF</td>
<td>Activity factor</td>
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<tr>
<td>APD</td>
<td>Accredited Practising Dietitian</td>
</tr>
<tr>
<td>ATP</td>
<td>Adenosine triphosphate</td>
</tr>
<tr>
<td>BDA</td>
<td>British Dietetic Association</td>
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<tr>
<td>BCM</td>
<td>Body cell mass</td>
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<tr>
<td>BIA</td>
<td>Bioelectrical impedance analysis</td>
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<tr>
<td>BMI</td>
<td>Body mass index</td>
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<tr>
<td>BMR</td>
<td>Basal metabolic rate</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>CO₂</td>
<td>Carbon dioxide</td>
</tr>
<tr>
<td>CPD</td>
<td>Continuing professional development</td>
</tr>
<tr>
<td>CV</td>
<td>Coefficient of variation</td>
</tr>
<tr>
<td>d</td>
<td>Day</td>
</tr>
<tr>
<td>DEXA</td>
<td>Dual-energy x-ray absorptiometry</td>
</tr>
<tr>
<td>DC</td>
<td>Direct calorimetry</td>
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<tr>
<td>DLW</td>
<td>Doubly labelled water</td>
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<tr>
<td>ECF</td>
<td>Extracellular fluid</td>
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<tr>
<td>EE</td>
<td>Energy expenditure</td>
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<tr>
<td>EN</td>
<td>Enteral nutrition</td>
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<tr>
<td>ER</td>
<td>Energy requirement</td>
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<tr>
<td>FAO</td>
<td>Food and Agriculture Organization</td>
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<tr>
<td>FFM</td>
<td>Fat free mass</td>
</tr>
<tr>
<td>FM</td>
<td>Fat mass</td>
</tr>
<tr>
<td>g</td>
<td>Gram</td>
</tr>
<tr>
<td>GIT</td>
<td>Gastrointestinal tract</td>
</tr>
<tr>
<td>HBE</td>
<td>Harris-Benedict equations</td>
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<tr>
<td>IBW</td>
<td>Ideal body weight</td>
</tr>
<tr>
<td>IC</td>
<td>Indirect calorimetry</td>
</tr>
<tr>
<td>icc</td>
<td>Intra-class correlation coefficient</td>
</tr>
<tr>
<td>ICU</td>
<td>Intensive care unit</td>
</tr>
<tr>
<td>IF</td>
<td>Injury factor</td>
</tr>
<tr>
<td>kcal</td>
<td>Kilocalorie</td>
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<tr>
<td>kg</td>
<td>Kilogram</td>
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</table>
kJ  Kilojoule (1kJ = 4.18kcal)
L  Litre
LBM  Lean body mass
m  Metre
MP&NC  Mouthpiece and noseclip
MJ  Megajoule
NSCLC  Non small cell lung cancer
O₂  Oxygen
PENG  Parenteral and Enteral Nutrition Group
PG-SGA  Patient generated subjective global assessment
PN  Parenteral nutrition
QUT  Queensland University of Technology
r²  Coefficient of determination (amount of variation explained)
REE  Resting energy expenditure
REEₘ  Measured resting energy expenditure
REEₚ  Predicted resting energy expenditure
RMR  Resting metabolic rate
RQ  Respiratory quotient
SCLC  Small cell lung cancer
SD (sd)  Standard deviation
SDE  Sedentary daily expenditure
SE (se)  Standard error
SGA  Subjective global assessment
SPSS  Statistical Package for Social Sciences
TBK  Total body potassium
TBW  Total body water
TEE  Total energy expenditure
TEF  Thermogenic effect of food
UNU  United Nations University
UUN  Urinary urea nitrogen
VCO₂  Carbon dioxide production
Vₑ  Minute ventilation
VH  Ventilated hood
VO₂  Oxygen consumption
WCCC  Wesley Cancer Care Centre
WHO  World Health Organisation
wt/W  Weight
Statement of Original Authorship

The work contained in this thesis has not been previously submitted for a degree or diploma at any other higher education institution. To the best of my knowledge and belief, the thesis contains no material previously published or written by another person except where due reference is made.

Signed: ________________________________

Date: _________________________________
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CHAPTER 1: INTRODUCTION

CONTENT

1.1 Introduction
1.2 Aims & Objectives
1.3 Thesis Orientation
1.4 Significance of the Thesis
1.1 Introduction

An understanding of patients’ energy requirements is necessary so that adequate and appropriate nutrition can be provided to the patient for their nutritional care and management. Provision of adequate nutrition support will ensure that patients attain and maintain a desirable body weight, improve nutritional status and avoid negative outcomes associated with over- or underfeeding. The success of nutrition support relies on accurately estimating energy requirements so that adequate energy and nutrients can be provided to the patient.

Warwick (1989) defines the energy requirement in healthy people as “the level of metabolisable energy intake from food that will balance energy expenditure, plus additional needs for growth, pregnancy and lactation: that is, the food energy required to maintain the status quo”. This definition defines energy requirement as that which is required for energy balance. Energy requirements have also been defined in terms of what is desirable for optimum health, that is, the energy requirement is:

...the level of energy intake from food that will balance energy expenditure when the individual has a body size and composition, and level of physical activity, consistent with long-term good health; and that will allow for the maintenance of economically necessary and socially desirable physical activity (FAO/WHO/UNU, 1985).

In the healthy individual, energy requirements can be summarised as:

\[
\text{Energy Requirements} = \text{Energy expended} + \text{Energy cost of growth} + \text{Energy cost of pregnancy} + \text{Energy cost of lactation}
\]

In a non-pregnant, non-lactating adult, energy requirements are primarily based on energy expenditure. The most accurate method for determining energy requirements is therefore by measurement of energy expenditure. These methods however are expensive, time-consuming, require trained technicians to perform them and are therefore impractical in the clinical setting. As such prediction equations are commonly used to estimate the energy requirements of hospitalised patients.

Personal communications with dietetic practitioners and personal experience during clinical practice identified several issues with respect to current methods for
determining patients’ energy requirements. There appeared to be variation in methods used between and within practitioners, and large inter-patient variability. Dietitians also appeared to lack confidence in the accuracy of prediction equations.

This Doctor of Philosophy research project therefore aimed to address two research questions - the first describing current methods used to determine patients’ energy requirements in general dietetic practice and the second relating specifically to energy expenditure in one disease state:

- How are patients’ energy requirements estimated in practice and what error or variation is introduced by these methods?
- Is energy expenditure altered in patients with cancer and what is the most appropriate method for determining the energy requirements of these patients?

Cancer was selected as the disease state to study as patients often experience significant weight loss, which is commonly believed to be associated with altered energy metabolism. Appropriate nutritional management of these patients is therefore essential.

1.2 Aims and Objectives

To address the research questions, this research project was separated into two phases. Phase 1 was a descriptive study to describe current dietetic practice in relation to estimating patients’ energy requirements. Having defined current practice, several issues were identified which required further investigation in an attempt to improve and clarify practice recommendations. Phase 2 therefore investigated practice-based issues relating to the estimation of resting energy expenditure in patients with cancer.

The aims and objectives for each phase are listed below. These aims and objectives are based on gaps in knowledge identified from the review of the literature (Chapters 2 and 4).

**Phase 1: Dietetic Practice**

**Aim** To describe current methods used by dietitians for estimating energy requirements of people with cancer.

1. To describe population groups for which Australian dietitians estimate energy requirements;
2. To identify the different prediction methods that Australian dietitians use in their daily practice;
3. To describe dietitians’ application of prediction equations and injury factors based on a given case study; and,
4. To describe the variability of the outcomes of the calculations.

Phase 2: Resting Energy Expenditure (REE) in Cancer

Aim To quantitatively investigate differences in energy expenditure of cancer patients compared to healthy controls.
1. To compare the measured resting energy expenditure of people with solid tumours to people without cancer (healthy control subjects).

Aim To compare different methods for determining energy requirements in people with cancer.
2. To investigate, in people with solid tumours and people without cancer, the accuracy of a new, portable device for measuring energy expenditure compared to a traditional validated method.
3. To compare the individual agreement of actual measurements of energy expenditure with estimates from prediction equations in people with solid tumours and people without cancer.
4. To compare the individual agreement between measurements of REE using different steady state criteria.

1.3 Thesis Orientation

This Doctor of Philosophy research project is presented as a Thesis by Publication. Five manuscripts (two published, one in press, one submitted and one in preparation) are included as components of the chapters in this thesis. All manuscripts have been accepted in, or submitted to, international peer-reviewed journals. Each manuscript is written in the conventional style for the journal, including reference style and spelling.

The thesis includes a comprehensive literature review, which has been presented in two separate chapters relating to each phase of the research project. Chapter 2 provides an introduction to energy expenditure and review of the literature relevant to Phase 1 on individuals’ energy requirements and current prediction methods.
available for estimating energy requirements. Manuscript 1, a review article, is included as part of chapter 2, and has been published in Nutrition Reviews (2003).

Phase 1 is described in detail in Chapter 3, including a description of the study design and research methods and presentation of the results. This chapter also includes Manuscript 2, based on the results of Phase 1, which has been published in the European Journal of Clinical Nutrition (2003).

Based on the results of Phase 1, several practice-based issues were identified for further investigation, which informed the development of Phase 2 of the research project. Chapter 4 includes a review of the literature relevant to Phase 2. This chapter critiques and discusses methods for measuring energy expenditure, approaches for analysing energy expenditure data and current research on energy expenditure in cancer.

Chapter 5 provides a detailed description of the methods undertaken for Phase 2 of the research project. A description of these methods is provided as a distinct chapter due to the limited ability to describe methodology in the published manuscripts. In establishing the methods for this study, methodological issues were encountered with respect to measurements of energy expenditure using the traditional indirect calorimeter (Objective 4). These were addressed in a measurement methods side study and are presented in Manuscript 3, as part of Chapter 5. This manuscript has been published in the Journal of Applied Physiology (2004).

Chapter 6 presents the results from Phase 2. This chapter includes first a description of the sample and comparison with the study population as this detail is not provided in the following manuscripts. The remainder of the chapter includes Manuscript 4 and Manuscript 5, presentation of additional results not included in the manuscripts and a discussion of the findings from this phase. Manuscript 4 addresses Objective 1 and 3 and is in preparation to be submitted to the British Journal of Cancer for consideration for publication. Manuscript 5 addresses Objective 2 of the research project and has been submitted to the European Journal of Clinical Nutrition for consideration for publication.

Manuscripts 3 to 5 present different results based on the same study design, with each manuscript designed to stand-alone. As such and to be expected, there is
some repetitiveness in the Introduction, Methods and Discussion sections of these three manuscripts.

An overall discussion linking together the findings from the two phases and from all five manuscripts, relating results to the overall aims and objectives is provided in Chapter 7. This chapter completes the thesis by drawing overall conclusions from the research project and providing recommendations for nutrition practice and future research.

1.4 Significance of the Thesis

i) Estimating patients’ energy requirements is a key component of dietetic practice

This study was the first to survey dietitians working in acute care adult hospitals throughout Australia, with respect to their current dietetic practice for estimating peoples’ energy requirements. A survey was conducted in 1998 which addressed methods used by dietitians working in children’s hospitals with intensive care units regarding the prediction of energy requirements of critically-ill children (White, 1998). The study was targeted at a specific study population and as such, the sample was relatively small. This current study aims to expand from the previous survey, targeting all dietitians working in acute care adult hospitals and addressing additional questions relating to factors that influence practice. This study is one of the largest known surveys of clinical dietetic practice in Australia to date. Defining current practice is the first step towards identifying areas that need improvement or changing. This study has the ability to influence the teaching and practice of methods for estimating patients’ energy requirements.

ii) The nutritional management of patients with cancer is a significant clinical issue

There is sufficient evidence to suggest that provision of appropriate and intensive nutrition support and counselling can assist patients with cancer to maintain weight and subsequently, improve nutritional status, quality of life and length of survival. Provision of appropriate nutrition support relies first and foremost on a knowledge and understanding of the patient’s energy requirement so that energy and nutrients can be adequately prescribed for the patient.
iii) Independent evaluation for the accuracy of new measurement devices in different population groups is essential for best practice

In the published literature, only one study, which was supported by a grant from the manufacturers, has validated a new portable device for measuring resting energy expenditure (MedGem™) in healthy people. To our current knowledge at the time of commencing this study, no other studies had attempted to investigate the accuracy of the MedGem device in adult patients with disease or injury. This study will be the first to validate the MedGem in people with cancer. In addition it is believed that the MedGem device used in this study is the first in Australia.
## CONTENT

2.1 Introduction
2.2 Components of Energy Expenditure
2.3 Factors Affecting Energy Expenditure
2.4 Intra-Individual and Inter-Individual Variation
2.5 Determining Energy Requirements
2.6 Manuscript 1: Predicting Energy Requirements in the Clinical Setting: Are Current Methods Evidence Based?
2.7 Additional Prediction Equations for Healthy Populations
2.8 Predicting Energy Requirements in Obese Subjects
2.9 Problems with Prediction Equations in Disease and Injury
2.10 Accuracy of Nutrition Support
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2.1 Introduction

In simple terms, energy requirement is the level of energy intake necessary to meet energy expenditure. This definition assumes that energy balance is desirable for optimum health, that is, the individual is of a healthy weight. Therefore for individuals with a weight that is above or below the desirable weight range, the energy requirement for good health would be less than or greater than total energy expenditure, respectively. To understand the energy requirement of individuals, knowledge of energy expenditure is necessary.

This chapter first provides a background on the components of total daily energy expenditure and factors that influence energy expenditure. A manuscript and further review of the literature that critically evaluate the scientific evidence on current methods for predicting energy requirements in different population groups and disease states is also included. The chapter concludes with a summary of the gaps identified in the current literature.

2.2 Components of Energy Expenditure

Total energy expenditure (TEE) is the amount of energy¹ (kilojoules or calories) used by the body over a 24-hour period. TEE is often considered in three components: basal metabolism, thermogenesis and physical activity. The contribution of each component to TEE differs among individuals. Figure 2.1 shows the typical contribution of each component to TEE.

2.2.1 Basal Metabolic Rate

Basal metabolic rate (BMR) is the minimum rate of energy necessary to support cellular function (Wong, et al, 1996) and is defined as "the energy expenditure of a subject after a 12-14 hour fast (usually overnight) and while mentally and physically at rest in a thermoneutral environment" (Warwick, 1989). Although BMR is not a fixed quantity, it forms the largest component of energy expenditure, accounting for approximately 50-80% of daily energy expenditure (Arciero, et al, 1993, Battezzati &

¹ Kilojoules (kJ) and calories (kcal) are used interchangeably throughout the thesis based on convention and country of publication from which the source is cited.
Figure 2.1: Typical relative contributions of components of total energy expenditure (Adapted from Toth, 1999)

The conditions necessary for accurately measuring BMR are sometimes difficult to achieve. As such, resting energy expenditure (REE, also referred to as resting metabolic rate, RMR) is often measured instead. REE is different from BMR in that it is not measured under strict basal conditions, such that the patient may not have fasted for 12-14 hours or may not be measured immediately upon wakening. It is well acknowledged that energy expenditure measured under resting conditions is approximately 10% higher than that measured under basal conditions (Kinney, 1983, Matarese, 1997, Turley, et al, 1993).

2.2.2 Thermogenesis
Thermogenesis relates to the changes in energy expenditure in response to a variety of factors such as food, cold, medications or hormones (Warwick, 1989). The thermogenic effect of food (TEF) contributes the greatest in healthy individuals, accounting for approximately 10-15% of energy expenditure (Mifflin, et al, 1990, Owen, et al, 1986). TEF refers to the energy associated with the digestion, absorption, transportation and storage of ingested nutrients (Frankenfield, 1998, Toth, 2001).

2.2.3 Physical Activity
Physical activity is the most variable of the components, typically accounting for approximately 20-30% of energy expenditure (Jequier & Schutz, 1983), but may
account for as little as 5% during bed rest or as much as 75% in elite athletes (Toth, 1999). Energy expenditure from physical activity varies within individuals from day-to-day and between individuals.

In practice, it is difficult to measure energy expended from physical activity. The energy expended when undertaking various levels of physical activity has been measured, and average values published (FAO/WHO/UNU, 1985). Average energy costs of physical activities are expressed as multiples of BMR, as the energy expended in physical activities is related to body weight (FAO/WHO/UNU, 1985, Warwick, 1989). However, it is not known whether the energy costs of modern day activities (including occupations) in Australia require the same physical effort as those that were derived from many years ago in Europe or in developing countries (Warwick, 1989). It is likely that modern day leisure activities and occupations require less energy expenditure due to greater advances in technology and less physical work, and more sedentary lives.

2.3 Factors Affecting Energy Expenditure

Several factors influence BMR and REE within and between individuals. Figure 2.2 shows a framework of factors influencing the components of TEE. The framework is based on the following literature review.

2.3.1 Body Surface Area

It is well accepted that body size and energy expenditure are related. Kleiber (1947) refers to work of Sarrus and Rameaux in 1839, later followed by Rubner in 1883, where these researchers first proposed the “surface law” after comparing the metabolic rates of animals. The surface law states that when expressed in relation to surface area, metabolic rate is constant (Davies & Cole, 2003). The law had a major impact on the concepts of energy metabolism and it was not long before reference standards for metabolic rate based on surface area were published (Boothby, et al, 1936, Fleish, 1951, Robertson & Reid, 1952).

Several problems with the theory emerged, including substantial variability both within and between species. In order to explain some of the observations, it was felt that in humans, factors other than surface area must determine metabolic rate:
Figure 2.2: Framework of factors influencing the components of total energy expenditure.
Solid line = known relationship; broken line = suggested relationship.
• The BMR/m² rises by about 75% between birth and 6 – 18 months and then falls by more than 30% in adult life;
• Women consistently have a lower BMR/m² than men;
• At thermoneutrality, a major change in surface area produced by altering the position of the body has little if any effect on metabolic rate (Elia, 1992).

### 2.3.2 Body Composition

Benedict (1915) reported that body surface area was an inadequate variable for expressing BMR, instead suggesting that the “mass of active protoplasmic tissue”, or the size of heat producing tissues, might be a better predictor. Subsequent researchers have also shown this to be true (Cunningham, 1980, Cunningham, 1991, Miller & Blythe, 1953). While body weight is the best measure of body size and accounts for significant variation in REE (Buchholz, et al, 2001, Mifflin, et al, 1990, Owen, et al, 1986, Taaffe, et al, 1995), the fat free mass (FFM) compartment of the body contains the organ and tissue components that are the most metabolically active.

Measurements of the REE of healthy individuals have shown that FFM is the single best predictor, accounting for approximately 60-90% of variation (R²) in REE (Table 2.1). That is, differences in the mass of FFM among individuals accounts for the greatest variation in REE. Variations in this statistic cannot be solely accounted for by differences in the method for assessing body composition, as there is variability when the same method has been used. For example, studies that have used dual energy x-ray absorptiometry (DEXA), a highly accurate method, have shown variations in R² from 0.64 to 0.92 (Table 2.1).

Fat free mass (FFM), lean body mass (LBM) and body cell mass (BCM) are different measurements used to define the mass of metabolically active tissues.

*Fat free mass:* is the mass of the body when ether-soluble material (fat tissue) has been removed. (Nelson, et al, 1992)

*Lean body mass:* is the mass of all tissues in the body excluding adipose tissue. (Adipose tissue is approximately 80% fat, 2% protein and 18% water). Also known as adipose tissue free mass. (Nelson, et al, 1992)
The difference between FFM and LBM is indicated in Figure 2.3. In a healthy individual the difference between these terms is small.

**Table 2.1: Proportion of variation ($R^2$) in resting energy expenditure explained by fat free mass (FFM) – comparison of studies**

<table>
<thead>
<tr>
<th>Reference</th>
<th>N</th>
<th>Females (%)</th>
<th>$R^2$</th>
<th>Body composition method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cunningham (1980)</td>
<td>223</td>
<td>46</td>
<td>0.70</td>
<td>Prediction equation</td>
</tr>
<tr>
<td>Webb (1981)</td>
<td>15</td>
<td>53</td>
<td>0.87</td>
<td>Densitometry</td>
</tr>
<tr>
<td>Ravussin et al (1989)</td>
<td>249</td>
<td>48</td>
<td>0.82</td>
<td>Densitometry</td>
</tr>
<tr>
<td>Astrup et al (1990)</td>
<td>10</td>
<td>40</td>
<td>0.91</td>
<td>BIA</td>
</tr>
<tr>
<td>Mifflin et al (1990)</td>
<td>482</td>
<td>51</td>
<td>0.80*</td>
<td>Skinfold thickness</td>
</tr>
<tr>
<td>Nelson et al (1992)</td>
<td>213</td>
<td>60</td>
<td>0.73</td>
<td>Densitometry</td>
</tr>
<tr>
<td>Arciero et al (1993)</td>
<td>522</td>
<td>37</td>
<td>0.90</td>
<td>Densitometry</td>
</tr>
<tr>
<td>Klausen et al (1997)</td>
<td>313</td>
<td>75</td>
<td>0.80</td>
<td>BIA</td>
</tr>
<tr>
<td>Sparti et al (1997)</td>
<td>40</td>
<td>50</td>
<td>0.90</td>
<td>Densitometry, DEXA</td>
</tr>
<tr>
<td>Gallagher et al (1998)</td>
<td>13</td>
<td>38</td>
<td>0.92</td>
<td>DEXA</td>
</tr>
<tr>
<td>Illner et al (2000)</td>
<td>26</td>
<td>50</td>
<td>0.92</td>
<td>BIA</td>
</tr>
<tr>
<td>Buchholz et al (2001)</td>
<td>58</td>
<td>48</td>
<td>0.85†</td>
<td>Deuterium dilution</td>
</tr>
<tr>
<td>Heymsfield et al (2002)</td>
<td>289</td>
<td>55</td>
<td>0.64</td>
<td>DEXA</td>
</tr>
</tbody>
</table>

BIA, bioelectrical impedance analysis; DEXA, dual energy X-ray absorptiometry.

* Weight best predictor for females; † Weight better predictor for females, fat mass significantly correlated for females.

**Figure 2.3: Body Compartments**

FM, fat mass; AT, adipose tissue; FFAT, fat free adipose tissue; LBM, lean body mass; FFM, fat free mass; RM, residual mass; SM, skeletal muscle

(Adapted from Heymsfield, et al, 2002)
Body cell mass: is equal to the difference between total cell mass and cell fat mass. BCM does not contain the extracellular fluid (ECF) component of FFM, which is relatively inert.


As it is generally considered that measurements of BCM are derived from more “pure” metabolically active tissues it could be assumed that BCM would account for greater variation in REE than FFM or LBM. Both Nielsen et al (2000) and Buccholz et al (2001) however found that BCM accounted for a smaller proportion of variation than FFM. This result may be due to the fact that BCM was deduced by subtraction of ECF from total body water rather than measured directly by use of total body potassium counting.

The relationship between REE and fat mass (FM) is less consistent than its relationship with FFM (Toth, 2001). FM is a relatively metabolically inert tissue, contributing to a small proportion of total BMR (Table 2.2). The proportion of variation in REE explained by FM varies in studies from as little as $R^2$ of one percent (Arciero, et al, 1993, Sparti, et al, 1997) to as much as 49 percent (Owen, et al, 1986). A number of studies have found a higher correlation of FM with REE in females compared to males (Buchholz, et al, 2001, Nielsen, et al, 2000, Owen, et al, 1986, Sparti, et al, 1997, Taaffe, et al, 1995), possibly due to the greater proportion of body weight as FM in females. Butte et al (1995) found a smaller amount of variation in BMR explained by FM in adults compared to infants and children, 10% versus 64% and 41%, respectively.

After adjustment for FFM, some studies have found no significant contribution of FM to REE (Klausen, et al, 1997, Owen, et al, 1987) while others have found a significant relationship (partial $r^2 = 2 – 22\%$) (Buchholz, et al, 2001, Nelson, et al, 1992, Nielsen, et al, 2000, Sparti, et al, 1997). Nelson et al (1992) found that FM improved the amount of variation in REE explained after adjustment for FFM, by approximately 4% and 5% for a group of males and females, respectively. When male and female subjects were pooled and stratified on the basis of body weight, the amount of variation explained by FM decreased to less than 1% for both lean and obese subjects (Nelson, et al, 1992). By grouping subjects based on weight categories, the variation in FM in the group is reduced; thereby possibly reducing it’s effect on REE.
2.3.3 Composition of Fat Free Mass

While FFM is the best predictor of REE, it does not account for all of the variation in REE, with approximately 20-40% of the variation remaining unexplained. Sparti et al (1997) hypothesised that the remaining variation in BMR of healthy individuals may be due to variations in the composition of FFM such as organ size and muscle mass, due to their differences in metabolic activity (Table 2.2). FFM is not composed of homogenous tissues and indeed can be separated into two distinct constituents – high metabolic rate and low metabolic rate tissues. Adipose tissue is often grouped with low metabolic rate tissues. In humans, the greatest proportion of REE (~60%) arises from organs such as liver, brain, heart and kidneys, which comprise only 5-6% of total body weight (Wang, et al, 2001).

Table 2.2: Organ and tissue metabolic rates

<table>
<thead>
<tr>
<th>Body Compartment</th>
<th>Organ/Tissue</th>
<th>Metabolic Rate kJ/kg (kcal/kg)</th>
<th>% Body Weight</th>
<th>% BMR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fat Mass</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adipose tissue*</td>
<td>19 (4.5)</td>
<td>21 – 33</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td><strong>Fat Free Mass</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skeletal muscle*</td>
<td>55 (13)</td>
<td>30 – 40</td>
<td>15 – 20</td>
<td></td>
</tr>
<tr>
<td>Organs†</td>
<td></td>
<td></td>
<td>5 – 6</td>
<td>60</td>
</tr>
<tr>
<td>Liver</td>
<td>840 (200)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brain</td>
<td>1004 (240)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart</td>
<td>1840 (440)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kidneys</td>
<td>1840 (440)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Residual†‡</td>
<td>50 (12)</td>
<td>33</td>
<td>15 – 20</td>
<td></td>
</tr>
</tbody>
</table>

* Low metabolic rate tissues; † High metabolic rate tissues; ‡ Residual tissues include bone, skin, intestine, glands

Adapted from Elia (1992)

The summary of energy expenditures per kilogram of organ mass for individual organs shown in Table 2.2 was derived from a limited number of carefully controlled studies, which measured oxygen consumption of individual organs and tissues *in vivo* through measurements of the difference in arterial and venous oxygen concentration across the tissue and measurements of blood flow (Elia, 1992, Holliday, et al, 1967). With recent advances in technology, further research using
magnetic resonance imaging (MRI) and positron emission tomography (PET) with 15-labeled oxygen ($^{15}$O$_2$) will be available for measuring organ size and metabolic rate (Heymsfield, 2002).

There are limited data regarding the metabolic rates and masses of different organs and tissues and only a few studies have investigated the effect of composition of FFM (organ masses) on REE. The methodologies of the studies to date, particularly with respect to the statistical analysis, do not appear directly comparable. The most plausible implication of these results however is a modest contribution of the composition of fat free mass (organ masses) to the amount of variation in REE explained (Gallagher, et al, 1998, Garby & Lammert, 1994, Illner, et al, 2000, Sparti, et al, 1997).

All of the studies investigating the effect of FFM composition on REE have assumed a constant organ metabolic rate across individuals and do not consider the potential intra-individual variation in organ metabolic rates, particularly in individuals with diseases (Heymsfield, 2002, Wang, et al, 2000, Wang, et al, 2001).

2.3.4 Gender

Measured metabolic rate is lower in females compared with males. It is generally believed that this difference in metabolic rate is accounted for by differences in FFM. For a given body weight and height females tend to have a greater proportion of body weight as FM and a smaller proportion as FFM than males.

When REE has been adjusted for FFM (including other variables such as FM, age, aerobic fitness), a persistent lower adjusted REE has been found in females compared with males. A clinically significant difference of 2-5% lower adjusted REE in females has been statistically significant in some studies (Arciero, et al, 1993, Ferraro, et al, 1992, Poehlman & Toth, 1995), but not in others (Buchholz, et al, 2001, Klausen, et al, 1997, Mifflin, et al, 1990, Owen, et al, 1987). Although this difference appears small, Ravussin et al (1988) showed that subjects who gained more than 10kg weight over a follow-up period of 21 $\pm$ 7 months (n=15), had a 4% lower adjusted REE (adjusted for FFM, FM, age and sex) at baseline compared to subjects who did not gain weight over that time period (n=111).

Energy expenditure in women also varies with phase of the menstrual cycle due to hormonal fluctuations. BMR and 24-hour energy expenditure (adjusted for FFM, FM,
age and physical activity) have been shown to be higher in females during the luteal phase of the menstrual cycle compared to females during the follicular phase (Ferraro, et al, 1992, Webb, 1986). Post-menopausal women appear to have similar adjusted energy expenditure to pre-menopausal women in the follicular phase of the menstrual cycle (Ferraro, et al, 1992, Klausen, et al, 1997).

2.3.5 Age
Similar to the relationship with gender, differences in FFM and measured metabolic rate are observed in people of different ages. Older people tend to have a smaller proportion of their body weight as FFM and a lower REE compared to younger people of the same body weight and height. A number of studies have found a lower adjusted REE in older subjects compared to younger subjects (Heymsfield, et al, 2002, Klausen, et al, 1997, Piers, et al, 1998, Poehlman & Toth, 1995). This finding suggests that the metabolic rate of tissues may be reduced in the elderly, particularly as it is the muscle mass component of FFM that is predominantly reduced with age (Battezzati & Vigano, 2001, Benedict, 1915, Piers, et al, 1998). Keys et al (1973) in their longitudinal study of metabolic rate in men indicated a reduction in BMR attributable to ageing of 1-2% per decade of age.

2.3.6 Genetics
A genetic influence has also been shown to account for some of the variation in BMR (Ravussin & Bogardus, 1989). Bogardus et al (1986) showed in their study of 130 Pima Indians from 54 families, 11% of the variation in BMR could be explained by family membership, independent of other most likely influencing factors (FFM, age and sex). Twin studies have also indicated a high intra-class correlation coefficient (icc) for measured BMR in monozygotic (identical) twins (icc = 0.8), compared to dizygotic twins (icc = 0.1) (Henry, et al, 1990). When adjusted for body weight and FFM the icc of dizygotic twins was still less than half that of monozygotic twins, supporting the hypothesis of a genetic influence on metabolic rate and energy expenditure. More recently, a number of different genotypes have been investigated for their potential effect on metabolic rate and energy expenditure (Kimm, et al, 2002, Walston, et al, 2003).

2.3.7 Ethnicity
The potential influence of ethnicity on REE was highlighted following Schofield’s (1985) observations that measured BMR of Indians was significantly lower for the same body weight than that predicted by European and American standards.
Factors including climate were investigated as possible explanations for the lower BMR of Indians. Recently, a study by Soares et al (1998) found that when BMR was adjusted appropriately for differences in body composition (refer to Section 4.5.1, page 112), no significant differences were observed between Indian and Australian men and women. These results do not provide any evidence for an ethnic influence on BMR.

2.3.8 Disease and Illness

Disease states can alter energy expenditure through any of the components of TEE. REE can be altered by diseases independent of body composition (Toth, 2001). A detailed discussion of the effect of disease and injury on REE is presented in Section 2.6 (Manuscript 1, pages 21-40) and Section 2.9 (pages 48-52). Heymsfield (2002) notes that alterations in REE may be due to either variation in the metabolic rates of individual organs and tissues or variations in the composition of FFM (i.e. proportion of high and low metabolically active cells).

2.4 Intra-individual and Inter-individual Variation

The BMR or REE of free-living individuals is remarkably constant. Intra-individual (within-subject) variation in BMR has a coefficient of variation (CV) of about 2.5-5%, excluding variation due to measurement error, with a lower CV (2.5 – 3.5%) found in studies of free-living subjects uncontrolled for diet and physical activity (Garby & Lammert, 1984, Gibbons, et al, 2004, Henry, et al, 1989, Soares & Shetty, 1986, Soares & Shetty, 1987) and a slightly higher CV (4.5 – 5%) found in controlled studies in calorimetry or respiration chambers (Astrup, et al, 1990, Murgatroyd, et al, 1987). The methods used for measuring BMR differed in these studies however the intra-individual variations observed were similar. This indicates that within-subject variation in BMR in healthy individuals, both young and old, is likely to be fairly constant irrespective of the measurement methods used.

Intra-individual variation in TEE, measured in calorimetry or respiration chambers, appears not to be as large as the variation in BMR, with a CV of 2% (Astrup, et al, 1990, Murgatroyd, et al, 1987). This difference however is likely to be due to the longer measurement period for TEE (24 hours) compared with 30-minute to 1-hour measurement periods for BMR. This CV for intra-individual variation in TEE however
does not represent the free-living individual where CV is likely to be greater due to
daily variations in physical activity and energy intake (effect on TEF).

The greatest variation in BMR is observed between individuals (inter-individual
variation), with CV of approximately 6%, after adjustment for differences in FFM

2.5 Determining Energy Requirements

Estimates of energy requirements should be based on measurements of energy
expenditure (FAO/WHO/UNU, 1985). As BMR is usually the largest component of
TEE, measurements of BMR or REE, which only require a short measurement time
(30 to 60 minutes), are generally preferred over measurement of TEE (24 hours).
Factors to account for physical activity and TEF are then incorporated into
measurements of BMR to estimate TEE (FAO/WHO/UNU, 1985).

Measurements of energy expenditure however are expensive and time consuming,
require trained personnel to perform them and are impractical in the clinical setting. As
such, prediction equations have been derived, as an alternative to actual
measurements, to estimate energy requirements in the clinical setting. These
equations are easy to use, inexpensive and universally available however their
accuracy is questionable (Flancbaum, et al, 1999). Although highly correlated with
BMR, FFM is difficult to measure in a clinical setting therefore many researchers
have developed prediction equations based on a number of easily measurable
1999, Webb & Sangal, 1991). Weight and/or height are often used in prediction
equations, with the addition of gender and/or age, to provide an estimate for an
individual’s FFM.

The following publication aimed to review the relative validity of commonly used
prediction equations and methods for healthy populations and in injury and disease.
2.6 Manuscript 1 – Predicting Energy Requirements in the Clinical Setting: Are Current Methods Evidence-Based?

Citation:

Date Submitted: July 2002

Date Accepted: September 2002

Contribution of authors:
MMR was the main author of the manuscript and conducted the review of the literature. SC supervised the research and assisted in the writing of the manuscript.

Please Note: The reference style for this manuscript is that appropriate for the journal.

The text of Manuscript 1 is not available online. Please consult the hardcopy thesis available from the QUT library.
The text of Manuscript 1 is not available online. Please consult the hardcopy thesis available from the QUT library.
\[ \text{Equation 2}\]

\[\text{Equation 3}\]

\[\text{Equation 4}\]

---

2 Refers to the amount of variation explained.
Chapter 2: Energy Requirements & Prediction Equations
Chapter 2: Energy Requirements & Prediction Equations
2.7 Additional Prediction Equations for Healthy Populations

The previous publication primarily focused on prediction equations commonly used in practice. Numerous other equations have been developed more recently based on healthy populations. Populations from which these equations have been derived are generally more representative of current populations in terms of an increased BMI. These equations however have not been readily adopted into practice – often due to their lack of validation in other population groups. These prediction equations include regression equations based on easily measurable variables as well as equations using actual measures of FFM (Table 2.3). Measurement of FFM is not readily available or easily measurable in the clinical setting and therefore may influence whether these equations can be adopted in clinical practice.

The Bernstein et al (1983) equations were derived from a sample of 48 male and 154 female overweight and obese subjects. The authors developed a number of regression equations based on different independent variables, including one based on age, height and weight. The coefficient of determination was moderate for the equation for males ($R^2 = 0.66$) and poor for females ($R^2 = 0.45$). No standard error of the estimate (SEE) to determine precision was reported and no external validation conducted.

The equations by Owen and colleagues (1987, 1986) for males and females are based on measurements of normal weight, overweight and obese subjects. These equations however, still tend to under represent the older population with only 8 (22%) females and 15 (25%) males over the age of 50 years studied. The amount of variation explain by the Owen equations is moderate ($R^2 = 0.55 – 0.56$) nevertheless an improvement on the Schofield equations ($R^2 = 0.36 – 0.53$). The approximated standard error for individual predictions however is quite large, 840kJ and 730kJ for male and female equations, respectively. In addition, the authors did not externally validate the equations. Instead the equations were internally validated in the population from which they were derived. This result is not surprising, yet has little benefit for promoting use of these equations in populations other than that in which it was derived.
### Table 2.3: Additional prediction equations from review of the literature

<table>
<thead>
<tr>
<th>First Author (Year)</th>
<th>Subjects</th>
<th>Equation</th>
<th>easily measurable variables</th>
<th>( R^2 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bernstein (1983)</td>
<td>48</td>
<td>M 40 ± 12.6</td>
<td>9.1 – 230.6% RMR (kcal/d) = 11.02 ( W ) + 10.23 ( H ) – 5.8 ( A ) – 1032</td>
<td>0.66</td>
</tr>
<tr>
<td></td>
<td>154</td>
<td>F 39 ± 12.0</td>
<td>above IBW RMR (kcal/d) = 7.48 ( W ) – 0.42 ( H ) – 3.0 ( A ) + 844</td>
<td>0.45</td>
</tr>
<tr>
<td>Owen (1987, 1986)</td>
<td>60</td>
<td>M 38 ± 15.6</td>
<td>28.2 ± 7.5 RMR (kcal/d) = 879 + 10.2 ( W )</td>
<td>0.55</td>
</tr>
<tr>
<td></td>
<td>36</td>
<td>F* 36 ± 12.6</td>
<td>29.4 ± 8.7 RMR (kcal/d) = 795 + 7.18 ( W )</td>
<td>0.56</td>
</tr>
<tr>
<td>Mifflin (1990)</td>
<td>251</td>
<td>M 44 ± 14.3</td>
<td>27( \dagger ) REE (kcal/d) = 10 ( W ) + 6.25 ( H ) – 5 ( A ) + 5</td>
<td>0.71</td>
</tr>
<tr>
<td></td>
<td>247</td>
<td>F 45 ± 14.0</td>
<td>26( \dagger ) REE (kcal/d) = 10 ( W ) + 6.25 ( H ) – 5 ( A ) – 161</td>
<td>0.71</td>
</tr>
<tr>
<td>Webb (1991)</td>
<td>24</td>
<td>M 33 ± 11.4</td>
<td>23.1 ± 5.7 SDE (kJ/d) = 118 ( W ) – 128(( W ) / ( H )( ^{1.6} )) + 3930</td>
<td>0.92</td>
</tr>
<tr>
<td></td>
<td>13</td>
<td>F 39 ± 13.3</td>
<td>25.1 ± 4.8 SDE (kJ/d) = 88 ( W ) – 110(( W ) / ( H )( ^{1.8} )) + 4406</td>
<td>0.74</td>
</tr>
<tr>
<td>Soares (1993)</td>
<td>121</td>
<td>M 18 – 60</td>
<td>&lt; 25.0( \ast ) BMR (kJ/d) = 48.7 ( W ) – 14.1 ( A ) + 3599</td>
<td>0.41</td>
</tr>
<tr>
<td>Cunningham (1980)</td>
<td>120( \circ )</td>
<td>M 29 ± 11.0</td>
<td>– REE (kcal/d) = 502 + 21.6 ( LBM )</td>
<td>0.7</td>
</tr>
<tr>
<td></td>
<td>103</td>
<td>F</td>
<td>–</td>
<td>( LBM )</td>
</tr>
<tr>
<td>Astrup (1990)</td>
<td>6</td>
<td>M 26 (22–47)</td>
<td>23.5 ± 1.6 BEE (kcal/d) = -74.4 + 32.3 ( LBM )</td>
<td>0.91</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>F 29 (23 – 45)</td>
<td>23.4 ± 2.1</td>
<td></td>
</tr>
<tr>
<td>Cunningham (1991)</td>
<td>212</td>
<td>M &amp; F</td>
<td>–</td>
<td>L &amp; ob REE (kcal/d) = 370 + 21.6 ( FFM )</td>
</tr>
<tr>
<td>Wang (2000)</td>
<td>212</td>
<td>M &amp; F</td>
<td></td>
<td>( FFM )</td>
</tr>
</tbody>
</table>

Where: BMI = body mass index; M = male; F = female; IBW = ideal body weight; W = weight (kg); H = height (cm); A = age (y); SDE = sedentary daily expenditure; FFM = fat free mass (kg); LBM = lean body mass (kg); L & ob = lean and obese

* Excluding 8 trained athletes; \( \ast \) Mean only (no SD provided); \( \dagger \) Included some with BMI < 18.5 kg/m\(^2\); \( \circ \) Based on data from Harris Benedict (1919)
BMR predicted by the Owen et al equations has been compared to measured BMR by other authors in a group of healthy males and females (Mifflin, et al, 1990) and in a group of older females (Taaffe, et al, 1995). In both studies, the Owen et al equations were more accurate than other prediction equations at predicting BMR. The mean difference (between predicted and measured) for females and males was –4% and –0.1%, respectively (Mifflin, et al, 1990). The mean difference for older females (mean age 67 ± 4.4yrs) was 2.2%, which is quite small considering this age group was underrepresented in the original study population (Taaffe, et al, 1995). Taaffe et al (1995) also examined the individual predictive accuracy of the equations and found that the Owen et al equations predicted individuals BMR in the order of ± 920 kJ/d (220 kcal/d, 17%) of measured BMR. More recently, Siervo et al (2003) found the Owen et al equation to be the most accurate (mean difference –0.75 ± 11.94%) in a group of 41 normal weight females (age 24 ± 3.8 yrs; BMI 22.8 ± 1.7 kg/m²).

Of the prediction equations shown in Table 2.3, the Mifflin et al (1990) equations have been based on the largest sample size (n=498). Their study included both normal weight and obese subjects (53% IBW 80 - 119%, 47% IBW ≥ 120%). The authors present two separate equations for gender that differ only with respect to the intercept. The equations have a high coefficient of determination (R² = 0.71) however the SEE is not reported and the authors did not externally validate the equations. Taaffe et al (1995) compared measured BMR to BMR predicted by the Mifflin et al equations in older females and showed a mean difference (between predicted and measured) of –3.9%, with limits of agreement in the order of ± 18% of measured BMR.

Webb and Sangal (1991) developed prediction equations to estimate sedentary daily expenditure (SDE) defined as 24 hour energy expenditure during quiet days of sedentary activity (refrained from exercise) including eight hours sleep and three regular meals. Two subjects recovering from burns were included in the study as the authors reported that the activities for these two subjects were similar to those described for the quiet day routine. These subjects had measurements conducted prior to discharge, had unhealed skin area less than 3% of body surface, were on standard diets and not taking any medications (Webb & Sangal, 1991). The inclusion of these two subjects with other presumably “healthy” subjects is questionable, due to the potential for ongoing effects of the injury on energy
expenditure in these subjects. Underweight, healthy weight, overweight and obese subjects were represented in the study. The older population again appears to be underrepresented, with only three (8%) subjects over 50 years of age. The coefficient of determination is high for both male and female equations ($r^2 = 0.74 - 0.92$), although the SEE is quite large and the equations have not been externally validated.

Soares et al (1993) developed prediction equations for Indian males. No overweight subjects were included in the analysis. The procedures under which the energy expenditure measurements were conducted are unclear. Although the amount of variation explained by the equation is low ($r^2 = 0.41$) the equation was externally validated in two separate Indian populations. The equation predicted the BMR for the groups within –0.4 to 1.6% of measured BMR. The equations were also externally validated in age-matched American and European subjects, with mean differences (between measured and predicted BMR) for the groups of 0.5% and 6.3%, respectively (Soares, et al, 1993). This is surprising, as prediction equations developed from predominantly Caucasian populations, such as the Schofield equations, have been shown by several authors to overestimate the energy expenditure of Indian subjects (Schofield, 1985, Soares, et al, 1998).

Cunningham (1980) was the first to propose a simple prediction equation with LBM as the single predictor of BMR. This equation was based on a re-analysis of data for 223 subjects from the studies of Harris and Benedict (1919). LBM was not measured in these subjects therefore Cunningham (1980) estimated LBM from prediction equations using height and weight. Limitations of the Harris-Benedict equations therefore also apply to these equations, in that they are not representative of current Western populations as subjects tended to be young and lean. Despite a high coefficient of determination ($R^2 = 0.70$) no SEE was reported and the author did not externally validate the equation. Subsequently, three separate studies compared BMR predicted by the original Cunningham equation with measured BMR indicating that the prediction equation tends to overestimate BMR. Mean differences between predicted and measured BMR were 10% and 3.2% for females and males respectively (Owen, et al, 1987, Owen, et al, 1986); 14% and 15% for females and males respectively (Mifflin, et al, 1990); and 13.7% for older females (Taaffe, et al, 1995). Furthermore, analysis of individual predictive accuracy indicated limits of agreement in the order of ± 20 – 25% (Owen, et al, 1987, Owen, et al, 1986, Taaffe, et al, 1995).
Astrup et al (1990) developed a prediction equation in a small number of young, normal weight subjects. The regression equation has a negative intercept, which is in contrast to a non-zero positive intercept observed in most studies (Cunningham, 1991, Wang, et al, 2000). The confidence interval (CI) for the intercept was not provided therefore it is not possible to determine whether it would be significantly different to other equations. Due to the small sample size of this study the CI is likely to be wide, however the intercept in other studies, where sample sizes are in the order of 100 – 400, range from 186 to 712 kcal (Cunningham, 1991). The equation however showed a high coefficient of determination ($r^2 = 0.91$), although it has not been validated in other populations.

Cunningham (1991) and more recently Wang et al (2000) have attempted to develop prediction equations based on a review of studies investigating the relationship between REE and FFM. Cunningham conducted a weighted mean calculation for 1483 observations (from seven studies), including both lean and obese subjects, to determine the intercept and slope for the regression equation. One of the equations included in this review is the original Cunningham equation (1980). Cross-validation studies however have indicated that this original equation overestimates REE particularly for females and therefore may invalidate its inclusion in this current study. Cunningham (1991) reports that the modified equation is likely to explain 85% of the variation in REE, however did not attempt to validate the equation in a healthy population. Taaffe et al (1995) compared predicted REE from the Cunningham (1991) equation to measured REE and observed a 3.3% mean difference between predicted and measured REE, which was considerably improved from the original Cunningham (1980) equation (mean difference 13.7%).

Similarly, Wang et al (2000) reviewed regression equations from 15 studies and calculated the mean slope and intercept to develop an REE-FFM prediction equation. Although not statistically rigorous, a theoretical whole body level modelling approach also indicated very similar values for the slope and intercept (Wang, et al, 2000). The authors did not attempt to externally validate the equation.

Wang et al (2000) report that variation in the intercepts and slopes of the regression equations reviewed in their study may be due to differences in methods for measuring FFM. The accuracy of these equations in practice is therefore likely to be dependent on the method used for assessing body composition in practice.
The list of prediction equations in Table 2.3 is by no means complete, but represents the array of equations available and hence the confusion in selecting the most appropriate prediction method. New prediction equations are regularly developed following invalidation of popular prediction methods, such as the Harris-Benedict equations, in specific population groups. Wang et al (2001) highlight this process of “cross-validation new formula development”, indicating the population specificity of prediction equations.

For prediction equations to be readily adopted in practice they must be validated in populations other than the population from which it was derived. Cross validation of the Owen et al (1987, 1986), Mifflin et al (1990) and possibly the revised Cunningham equation (1991) in other healthy population groups indicate that these equations may be appropriate to use in practice for estimating REE at the group level. Individual predictive accuracy however is still poor; therefore caution is needed when applying these equations to individuals. The original Cunningham equation (1980) does not appear appropriate for estimating REE. The equation by Wang et al (2000) requires external validation in other population groups before it can be recommended for use in practice.

2.8 Predicting Energy Requirements in Obese Subjects

Prediction equations commonly used in practice were based on lean (non-obese) subjects and therefore poses problems when these equations are used in our ever-increasing overweight and obese population (Australian Institute of Health and Welfare, et al, 2003). In overweight and obese subjects increases in body weight are primarily due to increases in FM, which is a relatively metabolically inert tissue. In overweight and obese individuals approximately 60-70% of excess body weight is FM and 30-40% is FFM (Foster, et al, 1988, Glynn, et al, 1999). Organ mass, the most metabolically active tissue, does not increase proportionally with increasing body weight in overweight adults. Therefore increases in REE are not directly proportional to increases in body weight. Equations that rely on body weight to determine energy requirements are likely to overestimate REE for obese subjects (Foster & McGuckin, 2001). This is particularly important if these equations are used to prescribe energy requirements for overweight or obese subjects, where further weight gain must be prevented.
A number of studies have attempted to cross-validate prediction equations in overweight and obese populations. Pavlou et al (1986) compared measured REE to predicted REE from the Harris-Benedict equations in 31 moderately obese men (BMI approximately 34 kg/m²). These authors found that while mean measured REE was 92 ± 10% of predicted REE, only 64% of patients measured REE fell within ± 10% of predicted REE (Pavlou, et al, 1986). Foster et al (1988) found similar results with their study of 80 moderately obese women (mean BMI 38.9 ± 7.4 kg/m²). Mean measured REE was 99.3 ± 12.2% of Harris-Benedict predicted however, only 59% of patients' measured REE was within ± 10% of predicted REE (Foster, et al, 1988).

Both of these studies investigated moderately obese subjects, while the study by Feurer et al (1983) investigated morbidly obese subjects. The latter group compared measured REE to REE predicted by the Harris-Benedict equations in 112 morbidly obese (mean BMI 48kg/m²) men and women (Feurer, et al, 1983). A significant difference between mean measured and predicted REE was observed (mean measured REE was 88.4% and 89.5% of predicted for men and women, respectively). At the individual level, only 39% of subjects' measured REE was within ± 10% of predicted.

These studies indicate the poor level of accuracy of the Harris-Benedict equations for predicting REE in individual obese subjects. The study by Feurer et al (1983) confirms the results of other studies indicating that the inaccuracy of prediction equations increases with increasing degree of obesity (Glynn, et al, 1999).

Two studies have measured REE in overweight and obese subjects and compared to REE predicted from a number of different prediction equations, including the Harris-Benedict, Owen et al, Mifflin et al, Cunningham and Bernstein et al equations, among others. Heshka et al (1993) studied 73 women and 53 men, with mean BMI of 35.2 ± 7.2 kg/m² and 41.5 ± 8.5 kg/m², respectively. Most of the equations overestimated REE for both obese men and women, with greater overestimation for men, most likely due to the higher BMI of male subjects. The Robertson and Reid equations (1952), based on body surface area, showed the smallest mean bias for predicted REE for men and women.
Equations based on body surface area were critiqued in the early 1900s due to their inappropriate measure of metabolically active tissue mass (see Section 2.3.1, page 11). Heshka et al (1993) provide possible explanations for the results of their study. The formula for calculating body surface area uses a power term, resulting in a curvilinear function. As opposed to regression equations of the linear relationship between weight and REE, which increase at a constant rate, a curvilinear relationship increases at a decreasing rate. This relationship is therefore more likely to represent increases in FFM that occur in obesity.

Siervo et al (2003) observed similar results in their study of 58 obese (mean BMI 34.9 ± 3.6 kg/m²) and 58 overweight (mean BMI 27.4 ± 1.4 kg/m²) women. For obese subjects, the Robertson and Reid (1952) equations were the most accurate (mean bias 0.66 ± 10.84%). For overweight subjects, the equations by Bernstein et al (1983) and Owen et al (1986) provided the best predictions of REE, mean bias 0.93 ± 10.32% and –3.74 ± 10.85%, respectively.

The use of actual body weight (ABW) in prediction equations based on weight will overestimate REE for overweight and obese individuals, as increases in FFM are not directly proportional to increases in body weight. The use of an “adjusted” body weight that more closely reflects body FFM is therefore often recommended. Several methods for adjusting body weight have been suggested – IBW + 25%(ABW – IBW) (Frankenfield, 1998); IBW + 50%(ABW – IBW) (Barak, et al, 2002, Glynn, et al, 1999). While Ireton-Jones and Turner (1991) recommend use of ABW rather than IBW for predicting energy expenditure, this applies to the authors’ regression equation but has not been validated for other prediction equations.

2.9 Problems with Prediction Equations in Disease and Injury

Individuals’ metabolic response to injury or disease is highly variable (Battezzati & Vigano, 2001, McClave, et al, 1999). McClave et al (1999) clearly highlight the problems with using prediction equations in injury and disease based on “the erroneous concept that patients will demonstrate a predictable, uniform, singular metabolic response to a given disease process”.
Disease states can alter energy expenditure independent of body composition. Hormones such as adrenaline, cortisol and glucagon are increased with stress, thereby increasing energy expenditure (Battezzati & Vigano, 2001). Immunological factors such as cytokines (e.g., interleukins, tumour necrosis factor, interferons) have also been shown to trigger the hypermetabolic response (Falconer, et al, 1994, Fearon, et al, 2001, Nelson, et al, 1994).

The metabolic response may be influenced by a number of factors, including individual patient variability, severity of disease, complications associated with the disease or pre-existing medical conditions (Battezzati & Vigano, 2001, McClave, et al, 1999). The variability in metabolic response is such that within a group of patients with the same disease some patients will be classed as hypermetabolic (increased REE), others classed as normometabolic (normal REE) and others classed as hypometabolic (decreased REE) when compared to a standard, most commonly REE predicted from Harris-Benedict equations.

Increases in energy expenditure with increasing numbers of co-morbid conditions is not necessarily a cumulative relationship (McClave, et al, 1999). Development and use of specific ‘injury factors’ for individual conditions (e.g., surgery, febrile, infection) may cause problems when predicting energy requirements if individual conditions are treated as multiplicative or additive, in terms of their effect on energy expenditure. Such practice may lead to gross overestimation of energy requirements, even more so with multiplication of factors compared to addition. Furthermore, since the development of the commonly used ‘injury factors’ (Long, et al, 1979, Wilmore, 1977), improvements in medical treatment such as mechanical ventilation, sedation, better wound care and control of ambient room temperature, have tended to decrease the effect of injuries and diseases on metabolic rate (Barak, et al, 2002, Elia, 1992, Frankenfield, 1998).

Recently Barak et al (2002) evaluated the ‘stress factors’ of hospitalised patients with various medical conditions. These authors proposed new ‘injury factors’ based on the ratio of measured REE to predicted REE by the Harris-Benedict equations (Table 2.4).

Almost 30% of patients studied had a BMI over 30kg/m². Adjustments for weight were therefore necessary for predicting REE from the Harris-Benedict equations to be comparable with normal weight subjects. The authors reported that using an
Table 2.4: Comparison of injury factors from the literature

<table>
<thead>
<tr>
<th>Disease/Condition</th>
<th>Wilmore 1</th>
<th>Long et al 2</th>
<th>Elia 3</th>
<th>ASPEN 4</th>
<th>Barak et al 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild Starvation</td>
<td>0.85 – 1.0</td>
<td>0.85 – 1.0</td>
<td>0.85</td>
<td>0.85</td>
<td>1.0</td>
</tr>
<tr>
<td>Minor surgery/elective operation</td>
<td>0.98 – 1.05</td>
<td>1.2</td>
<td>1.0 – 1.1</td>
<td>1.05 – 1.15</td>
<td></td>
</tr>
<tr>
<td>Surgery – complicated</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.25 – 1.45</td>
</tr>
<tr>
<td>Single fracture (eg long bone fracture)</td>
<td>1.14 – 1.25</td>
<td>1.0 – 1.1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple trauma (skeletal)</td>
<td>1.30 – 1.55</td>
<td>1.35</td>
<td>1.0 – 1.3</td>
<td>1.4</td>
<td></td>
</tr>
<tr>
<td>Sepsis/Severe infection</td>
<td>1.30 – 1.55</td>
<td>1.60</td>
<td>1.14 (fever 1°C)</td>
<td>1.20 – 1.40</td>
<td>1.30 – 1.35</td>
</tr>
<tr>
<td>Burns</td>
<td>1.25 (10%); 1.70; 2.10 (severe) (30%); 2.0 (50%); 2.13 (70%)</td>
<td>1.1 – 1.3 (10 – 2.0 (major) 25%, first month); 1.23 – 1.64 (25 – 90%, first month)</td>
<td>1.60</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Solid tumours</td>
<td></td>
<td></td>
<td>1.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inflammatory Bowel Disease</td>
<td>1.0 – 1.1</td>
<td></td>
<td>1.05 – 1.1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1 (Wilmore, 1977)
2 (Long, et al, 1979)
3 (Elia, 1990)
4 (Sax & Soub, 1998)
5 (Barak, et al, 2002)
adjusted weight defined as IBW (calculated from the Hamwi equation 1964) plus 50% of the difference between actual weight and IBW, produced similar ‘injury factors’ as normal weight and underweight patients (Barak, et al, 2002). This is only true if the stress response to disease and injury is the same in normal weight and obese subjects. To the investigator’s knowledge, there is no evidence to agree with or dispute this assumption.

An inherent problem with this study is that the data were analysed retrospectively based on measurements of REE that were conducted as part of standard hospital practice (n = 567). No consistent procedures were therefore undertaken for the measurements. Several conditions were not controlled for, which would inevitably affect the REE results:

1) 74% of patients for whom feeding state was recorded (n = 515) were fed during the measurement (enteral or parenteral nutrition);
2) 54% of patients for whom ventilatory state was recorded (n = 448) were mechanically ventilated;
3) 34% of patients for whom activity during measurement was recorded (n = 514) were moderately to very restless during the measurement; and
4) 23.6% of patients for whom temperature was recorded (n = 461) were febrile (>37.8°C) (Barak, et al, 2002).

Conditions 1, 3 and 4 would lead to overestimation of true REE while condition 2 would lead to underestimation of true REE. Measured REE for each medical condition were pooled regardless of feeding, ventilatory or febrile state or amount of activity during measurement. Derived ‘injury factors’ for each medical condition in this study are therefore associated with large standard deviations (approximately 15 – 20%, range 9 – 40%). Use of these ‘injury factors’ with the Harris-Benedict equations is likely to produce an even greater level of inaccuracy in the prediction of energy requirements of ill individuals.

Glynn et al (1999) conducted a similar retrospective analysis of measured REE in 57 hospitalised obese patients (mean age 54± 18y; mean BMI 34.5 ± 5 kg/m²). The authors reported that the Harris-Benedict equations using an adjusted weight calculated as IBW + 50%(actual – IBW) and an injury factor of 1.3 best predicted measured REE for the subjects studied (mean bias 8.9%; limits of agreement ± 12.1%), with 67% of predicted REE within ± 10% of measured REE. The patients studied however were by no means a homogenous group and measurements were
not conducted under standard or similar conditions – only 12% were fasting; 44% were ventilator dependent; diagnoses included cancer, pancreatitis, gastrointestinal disorder, trauma and pulmonary failure among others. These variations most likely account for the large mean bias (9%) and wide limits of agreement.

Often misconceived is the fact that increases in REE do not necessarily reflect an increase in TEE. In patients with disease or injury, the patients' capacity to undertake physical activity is usually limited, with patients often bed-bound or sedentary. Energy expenditure associated with activity is therefore reduced, often greater than the increase in REE thereby resulting in an overall reduction in TEE (Gibney, 2000, Toth, 1999, Toth & Poehlman, 2000).

2.10 Accuracy of Nutrition Support

The success of nutrition support relies on accurately estimating energy requirements so that adequate energy and nutrients can be provided to the patient (Roza & Shizgal, 1984). Due to the inherent problems with prediction equations, particularly in injury and disease, energy requirements may be incorrectly prescribed. Inappropriate nutrition support, both in terms of underfeeding and overfeeding, can have negative consequences for the health of the patient (Garrow, 1976, Klein, et al, 1998). Patient outcomes may be affected in terms of cost of treatment, rate of complications, increased length of hospital stay and mortality (Klein, et al, 1998).

2.10.1 Underfeeding

Underfeeding a patient will result in deterioration of nutritional status and weight loss. Such outcomes may be associated with poor wound healing, loss of body protein, increased risk of infection, and impaired organ function such as respiratory muscle function resulting in respiratory failure (McClave, et al, 1999, McClave, et al, 1998).

2.10.2 Overfeeding

Overfeeding may have negative effects on patient outcomes in terms of fluid overload, hyperglycaemia, hyperlipidaemia, hepatic dysfunction, azotaemia and respiratory distress (Klein, et al, 1998, McClave, et al, 1999, McClave, et al, 1998). Overfeeding with excess carbohydrate can cause hyperglycaemia and excess production of carbon dioxide (CO₂), resulting in poor blood glucose control and
respiratory distress (Elia, 1995). In mechanically ventilated patients, respiratory
distress can cause problems in weaning patients from the ventilator (Grant, 1994,
overfeeding are more common with parenteral nutrition compared to enteral nutrition

2.10.3 Optimal Feeding
It is unrealistic to expect each individual patient to be provided with nutrition support
that meets 100% of requirements. The inaccuracy of prediction equations
particularly for individuals indicates that this is unlikely. Even if REE is measured in
patients this level of accuracy may not be possible due to patient variation in energy
expenditure (eg day-to-day variation) as well as the need to estimate TEE from
measured REE to account for thermogenesis and activity.

Guidelines identifying the degree to which patients may be under or over fed while
avoiding complications of under- or overfeeding do not exist. More so, it is likely to
vary for each individual.

In Manuscript 1 it was reported that energy intake (energy provided) would need to
be within ±3-6% of energy requirements to maintain body weight within ±1kg over
three months. Siervo et al (2003) assessed the accuracy of each equation based on
a threshold level of a mean bias (between measured and predicted REE) of ±4%.
No rationale or evidence however was provided for this cut-off level. Amato et al
(1995) state that for a prediction formula to be useful, the mean absolute bias should
be within ±150 kcal (627 kJ) and the precision (limits of agreement) should be
within ±200 kcal (836 kJ). Precision in this study was defined as ±1 standard
deivation, which is in contrast to the ±2 standard deviations recommended by Bland
and Altman (1986). These values for bias and precision are based on the authors’
judgement for which no rationale is provided.

McClave et al (2003) investigated the clinical use of the respiratory quotient (RQ) as
a marker for under- and overfeeding and for monitoring adequacy of nutrition
support. Their study however indicated that measured RQ had poor sensitivity and
specificity thereby limiting its use as an indicator of under- and overfeeding. (RQ
discussed in more detail in Section 4.3, page 95). These authors recommend
comparing energy intake/provided with measured energy requirement as the most
appropriate method for determining adequacy of nutrition support (McClave, et al, 2003). However in many clinical situations and hospitals this option is not possible. Furthermore, other studies have shown that in a quarter to a third of cases, daily energy intake from delivered enteral nutrition is less than 90% of prescribed energy requirement (De Jonghe, et al, 2001, McClave, et al, 1998).

2.11 Summary

The ability to accurately determine the energy requirements of patients is vital to the provision of optimal nutrition support as part of nutritional care and management. The provision of appropriate nutrition support is necessary for people to attain and maintain a desirable body weight and improve nutritional status, while avoiding negative outcomes associated with under- or overfeeding. The nutritional goal of the stressed patient is to maintain energy balance (Battezzati & Vigano, 2001). Negative energy balance resulting in weight loss, in particular FFM, may be a significant predictor of morbidity and mortality (Kotler, et al, 1989, Tellado, et al, 1989).

Commonly used prediction methods for estimating energy requirements of healthy people are not based on data representative of current Western populations, have poor individual predictive value and have not been validated in other population groups. The inaccuracy of these equations is increased when applied to individuals with disease or injury, even when adjustments for the disease state have been included. Figure 2.4 summarises the methods currently used for estimating patients’ energy requirements.

Due to the poor predictive accuracy of current prediction methods it is commonly recommended that energy requirements be measured, not predicted, for individuals where an accurate energy requirement is needed (Amato, et al, 1995, FAO/WHO/UNU, 1985, Hunter, et al, 1988, Madden & Morgan, 1999, Warwick, 1989). In a clinical setting however measurement of energy expenditure is often not available or feasible. Elucidation of the degree to which energy intake can differ from energy requirement (% energy intake/ energy requirement) while still achieving nutritional care goals and avoiding complications associated with under- or overfeeding, is warranted.
Figure 2.4: Methods used in practice for estimating energy requirements
This review of the literature has identified several errors inherent with prediction methods including practice-based issues. An understanding of the methods used by dietitians in practice for estimating patients’ energy requirements, how these methods are applied and the variation in calculated energy requirement that results from current use of prediction equations, was therefore warranted.

The following chapter presents the objectives, methods, results and discussion of Phase 1 of this research project, which aimed to address dietetic practice issues identified from the literature.
# CHAPTER 3: DIETETIC PRACTICE (PHASE 1)

## CONTENT

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3.1 Introduction

Dietitians commonly use prediction equations to estimate patients’ energy requirements. Although practical and easy to use, the accuracy of these prediction equations is questionable. White (1998) conducted a survey of dietitians working in children’s hospitals with intensive care unit (ICU) facilities across Australia, to determine how energy requirements of critically ill children were calculated. Results of this survey indicated that inconsistent approaches used in the determination of energy requirements resulted in a large variation in calculated energy requirement (White, 1998). While this study has given some indication of dietitians’ practice, different prediction equations and methods are applied for estimating energy requirements for adults compared to children. No literature currently exists on how the energy requirements of hospitalised ill adults are estimated by dietitians in practice, either in Australia or overseas.

This chapter will firstly provide a detailed account of the research methods employed for Phase 1, a descriptive study, followed by the published manuscript based on the results of this study. This manuscript focuses primarily on the results of the case study section of the survey (described below). Additional results from the survey are presented after the manuscript. A summary of the findings from this Phase concludes the chapter.

3.2 Aims & Objectives

The aims and objectives addressed in this chapter relate to Phase 1 of the research project (refer to Section 1.2, page 3).

Aim To describe current methods used by Australian dietitians for estimating adult patients’ energy requirements.

1. To describe population groups for which Australian dietitians estimate energy requirements;
2. To identify the different prediction methods that Australian dietitians use in their daily practice;
3. To describe dietitians’ application of prediction equations and injury factors based on a given case study; and,
4. To describe the variability of the outcomes of the calculations.
3.3 Study Design

This descriptive study consisted of a cross-sectional mail survey of dietitians working in hospitals across Australia. This study design was thought to be the most appropriate method for obtaining relevant information from a large number of dietitians regarding their usual practice. The cross-sectional mail survey minimised the amount of resources (time and cost) required while still allowing for collection of relatively high quality data. Results of this study could also be compared to those of the single other identified survey regarding dietitians’ methods for estimating energy requirements (White, 1998).

3.4 Study Population

Dietitians work in a variety of settings, with the majority working in a hospital-based setting (Dietitians Association of Australia, 2001). To address the aims of the study, it was decided that only dietitians working in a hospital-based setting would be sampled. Dietitians working in hospital-based settings would be more likely to estimate energy requirements for acutely and chronically ill patients. However the exact number of dietitians working in this setting and the exact locations of where these dietitians work were unknown.

3.5 The Sample

3.5.1 Sample Size Calculations

As the study was descriptive and no hypotheses were being tested, no sample size calculations were performed. The aim of the study was to conduct a population survey, sampling as many dietitians from the study population as possible, so that the sample would be representative of all dietitians working in hospital-based settings.

3.5.2 Sampling Procedures

Since the exact number and location of dietitians working in hospitals were unknown, and hence the study population was not definable, a sampling frame of all
Australian hospitals was used to identify where dietitians might work rather than identifying individual dietitians themselves. A cluster sampling approach was therefore used, whereby dietitians were sampled from selected hospitals. The Australian Hospitals Directory (2000), the most recent at the time of the study, was used to identify hospitals, which would be likely to provide dietetic services, including both public and private hospitals.

**Inclusion Criteria**
Hospitals were selected if:
- the stated number of beds was greater than or equal to 100; or
- ‘Dietetics’ was listed under Allied Health Services provided by the hospital.

It was felt that hospitals with greater than 100 beds would be more likely to have a dietitian on staff compared to smaller hospitals based on professional knowledge of the location of services. The listing of ‘Dietetics’ under Allied Health Services provided could not be used solely as it was noted that hospitals that were known to the investigator to have several dietitians on staff did not include this information in their directory listing.

**Exclusion Criteria**
Hospitals were excluded if:
- they were rehabilitation or repatriation only hospitals; or
- they were children’s only hospitals

Rehabilitation and repatriation hospitals were excluded, as these hospitals are less likely to provide dietetic services or require the calculation of patients’ energy requirements, which was the aim of the study. Children’s only hospitals were also excluded as the study was targeted at identifying dietitians working with adult populations as the study by White (1998) had focused on children’s energy requirements.

### 3.5.3 Sample
From the directory, 226 hospitals across Australia were identified as the eligible sampling frame, including both public and private hospitals, metropolitan and non-metropolitan hospitals, and large and small hospitals. Hospitals were classed as metropolitan or non-metropolitan area based on postcodes according to Australia Post classifications (Australia Post, 2000).
As the study aimed to target dietitians within hospitals, each hospital was sent one survey per hundred beds. As such 528 surveys were initially posted to hospitals throughout Australia. Our intended initial sample was therefore 528 dietitians.

3.6 Survey Development

The aim of this survey was not only to collect information on methods dietitians use for a particular case study but also to look at the application of these methods and more broadly at usual dietetic practice with respect to estimating energy requirements. As no literature was identified on factors affecting dietitians’ practice in estimating patients’ energy requirements, an expert panel was formed to develop a preliminary framework of potential constructs and indicators.

The expert panel was based on a purposive sample of six dietetic professionals, of varying levels of experience and with both clinical and research experience. The investigator and supervisor (SC) facilitated the expert panel process. The process involved two consultations with the panel until consensus was achieved. Table 3.1 shows the preliminary framework of potential constructs and indicators derived from the expert panel consultation.

This preliminary framework together with the methods used in practice for estimating energy requirements (Figure 2.4) formed the basis of the development of the survey. The survey was divided into three sections – workplace and education details, a case study and usual dietetic practice (Appendix A). The survey was designed according to the criteria specified by Jackson and Furnham (2000) and Dillman (2000). These authors recommend using a booklet format, adhering to particular criteria regarding questionnaire format and design and cover letter, including a stamped addressed envelope for return of the survey (not reply paid), using multiple attempts to contact potential respondents, and offering to send a summary of the results.
Table 3.1: Preliminary framework of potential constructs and indicators affecting dietitians’ practice in estimating patients’ energy requirements

<table>
<thead>
<tr>
<th>What influences dietitians’ practice for estimating patients’ energy requirements?</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Education</strong></td>
</tr>
<tr>
<td>• When did they complete their dietetic education?</td>
</tr>
<tr>
<td>• Where did they complete their dietetic education?</td>
</tr>
<tr>
<td>• Are they committed to CPD?</td>
</tr>
<tr>
<td>• Are they an APD?</td>
</tr>
</tbody>
</table>

CPD = continuing professional development; ER = energy requirement; APD = Accredited Practising Dietitian

3.6.1 Workplace and Education Details
The first section was included to collect demographic details on respondents’ workplace (eg public or private hospital, number of beds) and dietetic education. This information allowed for the identification of potential characteristics or factors influencing dietetic practice as identified in Table 3.1.

3.6.2 Case Study
The case study was aimed to focus on a chronically and acutely ill adult as the study by White (1998) had investigated critically ill children. In developing the case study, the investigator consulted with two dietitians working closely with this type of patient, to ensure accuracy of information. The format of the case study was based on the survey used by White (1998). Additional questions were added to this section based on the framework for predicting energy requirements (Figure 2.4) and the ‘importance’ construct of Table 3.1.

The use of the case study method allowed comparison of our results with that from the study by White (1998). In addition, this method allowed for the identification of application and practical issues not otherwise elicited from multiple-choice questions.
3.6.3 Usual Dietetic Practice

The final section was used to identify broader issues associated with dietetic practice and estimating energy requirements. These questions were based on the ‘policy’, ‘familiarity’ and ‘importance’ constructs of Table 3.1. The last part of this section aimed to address a range of different prediction methods, both formal and informal methods identified by personal communications with dietetic practitioners. An additional prediction method was included as a “dummy” method (a real method however unlikely to be used by Australian dietitians) to provide some indication of potential response style bias (eg ‘yes-saying’ to items regardless of their content).

3.7 Piloting

The expert panel (Section 3.6, page 61) was again consulted to initially assess the survey for face validity (Are the questions relevant? Ambiguous?) and content validity (Do the questions comprehensively examine the aspects it is intended to measure?). Modifications were made to improve wording, to ensure correct interpretation of questions, and structure, by grouping questions into the three sections of the survey.

Following this initial consultation, the survey was piloted, for face validity, on a Queensland-based convenience sample. Informants were selected to reflect metropolitan and non-metropolitan areas and different levels of experience (managers and dietitians) (Table 3.2). It was felt that for the purpose of the pilot, convenience sampling of informants from Queensland rather than random sampling from the whole sampling frame, would not affect the construct and face validity of the testing.

Table 3.2: Description of convenience sample selected to pilot the survey

<table>
<thead>
<tr>
<th>Informants</th>
<th>Reason for Selection</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Dietetic Manager – Metropolitan Hospital</td>
</tr>
<tr>
<td>2</td>
<td>Dietetic Manager – Metropolitan Hospital</td>
</tr>
<tr>
<td>3</td>
<td>Dietitian – Metropolitan Hospital</td>
</tr>
<tr>
<td>4</td>
<td>Dietetic Manager – Non-Metropolitan Hospital</td>
</tr>
<tr>
<td>5</td>
<td>Dietitian – Non-Metropolitan Hospital</td>
</tr>
</tbody>
</table>
Based on the preliminary framework of factors influencing dietitians’ practice (Table 3.1), state differences would be reflected in different tertiary education institutions. The professional association however undertakes accreditation of all dietetic education courses and have set standards of key competencies that must be achieved (Dietitians Association of Australia, 1994). Differences between tertiary institutions and states are therefore likely to be minimal. It was thought that differences in geographical location (metropolitan and non-metropolitan area) however might affect indicators within the continuing professional development and policy constructs of the framework. State differences were believed to be less important than potential differences between metropolitan and non-metropolitan areas, hence the inclusion of these different areas in the selection of informants.

Informants were posted a copy of the survey to complete, along with a letter explaining the purpose of the pilot test and a short questionnaire regarding aspects of the survey and any comments. Four of the informants returned the completed survey and feedback questionnaire. Responses are presented in Table 3.3.

Table 3.3: Responses to feedback questionnaire on survey from convenience pilot sample (n=4)

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Does the cover letter clearly explain the aims of the survey?</td>
<td>4</td>
</tr>
<tr>
<td>Are the questions worded well?</td>
<td>4</td>
</tr>
<tr>
<td>Are the questions clear in what is being asked?</td>
<td>4</td>
</tr>
<tr>
<td>Is the typeface appropriate?</td>
<td>4</td>
</tr>
<tr>
<td>Is enough room provided for comments?</td>
<td>2</td>
</tr>
<tr>
<td>Do you feel it would be threatening to complete this survey?</td>
<td>0</td>
</tr>
<tr>
<td>Is the survey:</td>
<td></td>
</tr>
<tr>
<td>Too long?</td>
<td>1</td>
</tr>
<tr>
<td>Too short?</td>
<td>0</td>
</tr>
<tr>
<td>Appropriate length?</td>
<td>3</td>
</tr>
<tr>
<td>Approximately how long did the survey take to complete?</td>
<td>15 mins*</td>
</tr>
</tbody>
</table>

*All four respondents indicated 15 minutes to complete the survey

Based on the findings in Table 3.3 and written comments, minor formatting and stylistic changes were made. Written responses and comments to the survey appeared to indicate that questions were interpreted with the meaning that was intended. The length of the questionnaire remained the same and the cover letter...
included a statement that the survey should take approximately 15 minutes to complete. Final changes to the survey based on the pilot were presented to the original expert panel for agreement. Finally substantial formatting changes were made to improve the presentation of the survey. Surveys were professionally printed.

### 3.8 Procedure

Five hundred and twenty-eight surveys were initially posted to 226 hospitals throughout Australia. A cover letter, addressing the aim of the survey and the research project, was supplied with each survey, along with a form to complete if respondents wanted to receive a summary of the findings from the study and a stamped addressed envelope, to encourage responses (Appendix B). Surveys and return envelopes were coded and the codes recorded for surveys sent to each hospital. Codes were used to assist in identifying hospitals where dietitians had not responded so that follow-up surveys could be posted and characteristics of non-respondents could be compared with respondents (hospital type, metropolitan status).

For hospitals where multiple surveys were sent, an additional letter to the Director of the department was included, explaining the purpose of the survey and requesting distribution of the surveys to dietitians in the department (Appendix B). Directors were also asked to return any spare surveys if more had been sent than the number of dietitians in the department, to assist in determining the sample size.

Two weeks after the initial posting, a reminder letter was sent to all hospitals to encourage responses (Appendix B). At this time, hospitals which had not stated that they provided ‘Dietetic’ services according to the Australian Hospitals Directory (2000), but were included in the study (due to greater than 100 beds), and had not yet responded were contacted by phone to ascertain whether any dietitians worked at the hospital. The sample size was adjusted accordingly (Table 3.4).

Four weeks later (six weeks after the initial survey), a second copy of the survey, and cover letter (Appendix B) was sent to hospitals where surveys had not yet been returned, to further encourage responses.
Table 3.4: Estimated sample size and response rate to survey

<table>
<thead>
<tr>
<th>Total number of surveys sent</th>
<th>528</th>
</tr>
</thead>
<tbody>
<tr>
<td>Returned surveys (extras)</td>
<td>-35</td>
</tr>
<tr>
<td>Non-returned surveys (extras)*</td>
<td>-10</td>
</tr>
<tr>
<td>Phone call (no dietitians)†</td>
<td>-22</td>
</tr>
<tr>
<td>Extra survey completed</td>
<td>+3</td>
</tr>
<tr>
<td><strong>Total Sample Size</strong></td>
<td>464</td>
</tr>
<tr>
<td><strong>Total number of completed surveys</strong></td>
<td>307</td>
</tr>
<tr>
<td><strong>RESPONSE RATE</strong></td>
<td>66.2%</td>
</tr>
</tbody>
</table>

* Where the returned surveys indicated that the number of dietitians on staff was less than the number of surveys posted to the hospital (spare surveys were not returned).
† Phone calls to hospitals identified 22 hospitals with no dietitians – only one survey sent to each of these hospitals

### 3.9 Statistical Analysis

Statistical analyses were carried out using SPSS for Windows (Version 11.0.1, 2001, SPSS Inc, Chicago). Distributions of categorical variables are presented as counts (percentages). Continuous variables are presented as means ± standard deviation (sd), when Normally distributed, or median (range), for variables not Normally distributed. In the usual dietetic practice section of the survey, which included yes/no questions, some respondents made additional comments of “sometimes” or “occasionally”. For the purpose of the survey these have been coded as “yes”.

Bivariate statistical summaries and corresponding statistical analyses were conducted in an attempt to gauge a preliminary understanding of characteristics affecting estimates of energy requirements. Although all comparisons attaining statistical significance are reported here, these were also supplemented by reported comparisons of clinically meaningful differences, due to the lack of _a priori_ power calculations.

One-way analysis of variance (ANOVA) was used to compare calculated energy requirement with characteristics of the hospital (public v private, sole dietitian v others, bed size), education institution (also Australia v overseas), method used and...
short-term nutritional care goals. ANOVA was also used to compare the amount of
time spent working in a hospital with the method used, frequency of calculating
energy requirements, and a range of different methods for estimating energy
requirements (formal and informal). Pearson’s correlation coefficients were used to
assess the relationship between calculated energy requirement and the amount of
time working in a hospital and between calculated energy requirement and the
importance rating of the calculation.

Fisher’s Exact tests were used to compare respondents and non-respondents with
characteristics of the hospital (type and location). This test was also used to
compare the methods used and the importance rating with characteristics of the
hospital (public versus private, sole dietitian versus working with others, bed size)
and place of dietetic education. The frequency of calculating energy requirements
was compared to characteristics of the hospital (public v private, sole dietitian v
others, bed size) using Fisher’s Exact tests. Statistical significance was set at the
conventional 95% level (two-tailed).

As a cluster sampling approach was used for identifying dietitians, design effects
were calculated using the SUDAAN statistical package (Version 7.5, 1997, North
Carolina). These analyses produced cluster design effects ranging from 0.89 to
1.22, indicating minimal effect of cluster on results. That is, respondents within
clusters (hospitals) responded no more similarly than respondents between
hospitals. As cluster sampling design had only this negligible effect on the results,
the manuscript and other results presented herein are based on simple descriptive
and bivariate analyses, ignoring the clustering effect.

3.10 Ethical Considerations

This study was considered by the QUT University Human Research Ethics
Committee to be exempt from full ethical clearance (Ref No: 2396H). It was
approved that implied consent would be evident through completion and return of
the survey.
3.11 Manuscript 2 – Variation in the application of methods used for predicting energy requirements in acutely ill adult patients: a survey of practice.

Citation:

Date Submitted: November 2002

Date Accepted: January 2003

Contribution of authors:
MMR was the main author of the paper, initiated and designed the study, carried out statistical analyses, interpretation and discussion of results. SC assisted in design of the study, interpretation and discussion of results and contributed to writing the paper.

Please Note: The reference style for this manuscript is that appropriate for the journal.

Manuscript 2 is not available online. Please consult the hardcopy thesis available from the QUT library
Manuscript 2 is not available online. Please consult the hardcopy available from the QUT library.
3.12 Additional Results & Discussion – Usual Dietetic Practice

The following results are based on the Usual Dietetic Practice section of the survey (Appendix A). These results were not presented in the manuscript as the focus there was primarily on results from the case study.

The majority of respondents reported typically calculating energy requirements for patients on a daily to weekly basis (Table 3.5). Analysis for statistical and clinical significance of the data indicated that the frequency of calculating patients’ energy requirements did not differ with the amount of time spent working in hospital settings (hospital experience).

Table 3.5: How often dietitians typically calculate energy requirements for any patients/clients (n = 298)

<table>
<thead>
<tr>
<th>Frequency</th>
<th>N</th>
<th>%</th>
<th>Hospital Experience (years)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>More than 1/day</td>
<td>91</td>
<td>30.5</td>
<td>7.8 ± 0.7</td>
</tr>
<tr>
<td>Less than 1/day but greater than 1/week</td>
<td>115</td>
<td>38.6</td>
<td>8.2 ± 0.7</td>
</tr>
<tr>
<td>Less than 1/week but greater 1/month</td>
<td>73</td>
<td>24.5</td>
<td>9.3 ± 0.9</td>
</tr>
<tr>
<td>Less than 1/3 months</td>
<td>19</td>
<td>6.4</td>
<td>9.0 ± 1.9</td>
</tr>
</tbody>
</table>

* mean ± standard error

Respondents were also asked to indicate the types of patients for whom they currently estimate energy requirements (with the choice of selecting more than one type) (Table 3.6). Almost all (97.7%) respondents estimate energy requirements for patients receiving enteral nutrition. In comparison, only 56.9% of dietitians reported estimating energy requirements for patients receiving parenteral nutrition. It is likely that this is an underestimate, as generally only a small proportion of dietitians regularly see patients receiving parenteral nutrition. Respondents also indicated estimating energy requirements for patients requiring weight gain (67.1%) and those who are critically ill (54.9%) or recovering from trauma (43.6%).
Table 3.6: Patients/clients for whom dietitians currently estimate energy requirements (n = 307)

<table>
<thead>
<tr>
<th>Patient type</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Receiving enteral nutrition</td>
<td>300</td>
<td>97.7</td>
</tr>
<tr>
<td>Requiring weight gain</td>
<td>206</td>
<td>67.1</td>
</tr>
<tr>
<td>Receiving parenteral nutrition</td>
<td>168</td>
<td>56.9</td>
</tr>
<tr>
<td>Critically-ill</td>
<td>163</td>
<td>54.9</td>
</tr>
<tr>
<td>Recovering from trauma</td>
<td>129</td>
<td>43.6</td>
</tr>
<tr>
<td>Requiring weight maintenance</td>
<td>70</td>
<td>22.9</td>
</tr>
<tr>
<td>Requiring weight loss</td>
<td>58</td>
<td>19.0</td>
</tr>
<tr>
<td>Other</td>
<td>29</td>
<td>9.4</td>
</tr>
</tbody>
</table>

Finally, respondents were asked to indicate, from a list of different prediction methods (including formal calculations and informal methods) which methods they use and for whom or when they would use it (Table 3.7). Types of patients and situations for when these methods are used are ranked based on the most frequently reported from written responses. No respondents indicated using the “dummy” method in practice (as expected amongst Australian dietitians), providing some evidence that respondents were not influenced by response style (‘yes-saying’) bias.

Results shown in Table 3.7 confirm results presented in the manuscript (Section 3.11, pages 68-82) and in Table 3.6. The Schofield equations were the most frequently reported prediction method. Enteral nutrition and parenteral nutrition were the most common situations for using formal prediction methods (Schofield equations and Harris-Benedict equations) for estimating energy requirements. Choice between these two equations appears to be determined by the amount of information available on the patient (e.g., weight and/or height).

Current intake with adjustments was most frequently reported for use with patients requiring weight loss or weight gain. It is accepted that an energy deficit of 500kcal/d is associated with a weight loss of 0.5kg per week (National Health and Medical Research Council, 2002, National Heart Lung and Blood Institute Obesity Education Initiative Expert Panel, 1998). Likewise an excess of energy intake is associated with a similar weight gain. If the deficit or surplus however is based on the reported intake, this method relies on the accuracy of the dietary intake method.
### Table 3.7: Different prediction methods used by dietitians in practice

<table>
<thead>
<tr>
<th>Prediction method</th>
<th>N (%)</th>
<th>Types of Patients or Situations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schofield equations</td>
<td>278 (90.6%)</td>
<td>Enteral nutrition/ Parenteral nutrition</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No height available/known</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Weight gain/malnutrition</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Critically ill/ ICU</td>
</tr>
<tr>
<td></td>
<td></td>
<td>All/most patients</td>
</tr>
<tr>
<td>Current intake ± adjustments</td>
<td>184 (59.9%)</td>
<td>Weight gain/underweight/poor intake</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Weight loss</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diabetes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Outpatients</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Enteral nutrition/Parenteral nutrition</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Weight maintenance</td>
</tr>
<tr>
<td>Harris Benedict equations</td>
<td>146 (47.6%)</td>
<td>Enteral nutrition/Parenteral nutrition</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Height and weight known/available</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Weight gain</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ICU/Critically ill/Trauma</td>
</tr>
<tr>
<td>kcal/kg or kJ/kg</td>
<td>143 (46.6%)</td>
<td>Paediatrics/children/infants/babies</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Renal disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Critically ill/ICU</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Enteral nutrition/ Parenteral nutrition</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Comparing with other methods</td>
</tr>
<tr>
<td>Eyeball &amp; guestimate</td>
<td>127 (41.4%)</td>
<td>Missing information (eg weight/height)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Weight gain/poor nutritional status</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Weight loss</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Time constraints/ “in a hurry”</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Not critical/non-urgent/rough estimate</td>
</tr>
<tr>
<td>Standard value</td>
<td>40 (13.0%)</td>
<td>Elderly</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Weight loss</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CVA/Stroke</td>
</tr>
<tr>
<td>Wilmore nomogram</td>
<td>8 (2.6%)</td>
<td>Injury factors – Enteral nutrition/ surgery/ ventilated/ burns/ trauma/ ICU</td>
</tr>
<tr>
<td>Ireton-Jones equations</td>
<td>4 (1.3%)</td>
<td>ICU/ventilated patients</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Critically ill</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Obese – compare to other calculations</td>
</tr>
</tbody>
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ICU = intensive care unit; CVA = cerebral vascular accident
Respondents reported most commonly using the kcal/kg method with paediatrics. This thesis has focused on the energy requirements of adults and therefore comments as to whether this method is appropriate for this age group is beyond the scope of this thesis. Textbooks and reference materials commonly recommend use of this method in renal disease and ICU patients (A.S.P.E.N. Board of Directors and The Clinical Guidelines Task Force, 2002, Wilkens, 1996).

Use of an informal eyeball method was also reported. This method is often used in situations where important information for calculating energy requirements from formal prediction methods (for example, weight and/or height) is not available. In these situations the practitioner usually scans the patient to get an estimate of their weight and/or height and makes a “guestimate” of their requirement. Respondents reported that this method may be commonly used for patients requiring weight gain or weight loss. This is likely to be based on a similar principle to the “current intake ± adjustments” method.

3.13 Summary

This study appears to be one of the largest identified surveys of current dietetic practice in Australia to date (Collins, 2003). The survey by White (1998) targeted a specialised sample of dietitians for which the survey was directly relevant and achieved a response rate of 62% (n=49). The response rate of 66% (n=307) in this study is comparable.

This study aimed to determine current methods used by dietitians for estimating patients’ energy requirements by (a) determining population groups for which Australian dietitians estimate energy requirements; (b) identifying the different prediction methods that Australian dietitians use in their daily practice; (c) investigating dietitians’ application of prediction equations and injury factors; and (d) estimating the variability of the outcomes of energy requirement calculations.

To address the aim and objectives a survey was developed based on a preliminary framework for assessing factors that influence dietitians practice for estimating patients’ energy requirements. Results of the survey indicated that dietitians regularly estimate patients’ energy requirements in their daily practice. Other findings were that energy requirements are primarily estimated for patients receiving
enteral feeding whereas few dietitians estimate requirements for patients requiring weight loss or weight maintenance. Dietitians reported that the methods used for estimating patients’ energy requirements were primarily influenced by those taught to them in their initial dietetic education.

A number of different prediction methods are used to estimate patients’ energy requirements. Choice between formal and informal calculations appears to be influenced by the patient type or situation, such that formal calculations are commonly used for patients requiring enteral or parenteral nutrition and malnourished or critically ill patients. Informal methods are generally used for patients requiring weight loss or gain.

Calculation of the energy requirement for the case study indicated varied practice and inconsistencies in the approaches used and application of methods, in particular injury factors. The lack of consensus in the methods used for estimating the energy requirement for the case study corresponded in a large range of calculated energy requirements by the respondents. This variation in estimations tends to indicate that there is error inherent with the use of prediction methods, which may result in negative outcomes associated with underfeeding or overfeeding.

This phase sought to describe current practice so that issues or problems identified would inform the remainder of the research project. This survey identified a number of practice-based issues with the use of traditional prediction methods. Application of these commonly used methods failed to produce estimates of energy requirements within an appropriate level of accuracy. Lack of a true measurement of energy expenditure for the case study limited the extent to which the degree of error could be quantified.

The findings of this study therefore suggest the need to identify more appropriate methods for determining patients’ energy requirements in a clinical setting, whether these methods be more recently developed prediction equations or new practical measurement tools. To determine the accuracy of new methods, actual measurement of energy expenditure using a valid method would be required. Application of prediction methods, particularly injury factors for the cancer case study provided indicated inconsistencies or perhaps a lack of understanding of the effect of cancer and its treatment on energy requirements.
The following chapter provides a review of the literature relating to the measurement of energy expenditure, appropriate analysis of energy expenditure data and energy expenditure in patients with cancer. Results of Phase 1 in combination with the literature review led to the development of Phase 2 of the research project.
CHAPTER 4: ENERGY EXPENDITURE – MEASUREMENT, ANALYSIS & CANCER AS A CASE STUDY (LITERATURE REVIEW)

CONTENT
4.1 Measurement of Energy Expenditure
4.2 Direct Calorimetry
4.3 Indirect Calorimetry
4.4 Doubly Labelled Water
4.5 Analysis of Energy Expenditure Data
4.6 Cancer-Induced Weight Loss and Cancer Cachexia
4.7 Energy Expenditure in Cancer
4.8 Measurement of Body Composition
4.9 Summary
4.1 Measurement of Energy Expenditure


Energy used by the body is derived from energy containing macronutrients consumed in the diet. Food energy is stored as chemical energy in carbon-hydrogen bonds, however cells within the body cannot utilise this energy in its direct form (Sherwood, 1997, p.28). Instead energy from macronutrients must be converted into a form of energy they can use. Glucose is the preferred energy source for cells. Cellular oxidation of glucose and the release of energy, via a high-energy phosphate bond, most commonly in the form of adenosine triphosphate (ATP) are briefly described.

Once transported to cells through the blood, glucose is broken down via glycolysis, an anaerobic reaction, which yields only two molecules of ATP. The end products of glycolysis (two pyruvic acid molecules) are further broken down in the mitochondria to acetic acid, producing one molecule of carbon dioxide (CO₂) and releasing a hydrogen atom. Acetic acid combines with coenzyme A to produce the compound acetyl coenzyme A (acetyl CoA) and enters the citric acid cycle, a series of eight separate biochemical reactions during which two carbon atoms are cleaved and released in the form of CO₂, an ATP molecule is released and hydrogen atoms are captured by hydrogen carrier molecules. At this point, only four molecules of ATP have been produced per molecule of glucose.

Hydrogen carrier molecules enter the electron transport chain, which releases the high-energy electrons from the hydrogen atoms to the electron carrier molecules. As the high-energy electrons fall to lower energy levels with each step of the chain energy is released. Part of this released energy is lost as heat while the remainder is used to synthesise ATP, through the activation of the ATP synthetase enzyme, which converts a molecule of adenosine diphosphate (ADP) and inorganic phosphate (Pᵢ) to ATP. An additional 32 molecules of ATP are yielded from transport through the electron transport chain.
Once formed, ATP is transported out of the mitochondria and is available as an energy source as needed. ATP therefore acts as an energy reservoir, storing energy temporarily until the high-energy phosphate bond is hydrolysed in energy requiring reactions, producing ADP and P\. There are several processes within the body that require energy – synthesis of new chemical compounds (biosynthesis) such as protein synthesis, membrane transport such as active transport, and mechanical work such as contraction of the heart or skeletal muscles (Groff, et al, 1995, p.57, Sherwood, 1997).

The chemical pathways described above can be simplified into the reactions shown in Figure 4.1. In this figure, substrate metabolism at the cellular level is equivalent to the breakdown of glucose via glycolysis, the citric acid cycle and the electron transport chain. Gas exchange across the lungs is necessary for uptake of oxygen, which is a reactant in the electron transport chain, and output of carbon dioxide, which is produced in the breakdown of pyruvic acid and the citric acid cycle. Heat released is that produced in the electron transport chain and the ultimate end product is ATP. Several methods have been developed for measuring energy expenditure, which either directly or indirectly measure energy expenditure through different processes within these reactions.

This figure is not available online. Please consult the hardcopy thesis available from the QUT library.

Figure 4.1: Cellular metabolism, heat production and gas exchange
(Frankenfield, 1998)
This chapter reviews the literature regarding different methods for measuring energy expenditure including both traditional and new methods, appropriate methods for analysing energy expenditure data and critiques the current literature on energy expenditure in cancer. The chapter also includes a brief review on methods for measuring body composition, which is necessary for analysing energy expenditure data and concludes with a chapter summary highlighting the gaps in the current literature.

4.2 Direct Calorimetry

The most accurate method for measuring energy expenditure is by direct measurements of heat losses via direct calorimetry (Figure 4.1). Direct calorimeters measure both sensible heat loss (radiative and convective) and evaporative heat loss (McLean & Tobin, 1987, p.120, Murgatroyd & James, 1980, Pittet, 1980, Wilmore, 1977, p.7). For total heat loss to equal total heat production, and thus total energy expenditure, direct calorimetric measurements must be taken over 24 hours, to account for heat storage (Jequier, 1980). Heat is stored within the human body and as such an increase in heat production is not immediately followed by a corresponding increase in heat release.

Direct calorimeters can be classified as isothermal (gradient layer), heat-sink, convection or differential. The different types of direct calorimeters differ according to the means of measuring heat transfer (McLean & Tobin, 1987, p.122). Modern direct calorimeters for measuring energy expenditure in humans operate on either the isothermal or heat-sink principle, described in more detail below (Figure 4.2).

![Figure 4.2: Schematic diagrams of two types of direct calorimeters](image)

This figure is not available online. Please consult the hardcopy thesis available from the UQT library.

Figure 4.2: Schematic diagrams of two types of direct calorimeters
(a) Isothermal; (b) Heat-sink. $\Delta T$ is change in temperature across the layer; $T_{wi}$ is temperature of input water; $T_{wo}$ is temperature of output water; $V_{water}$ is volume of water. (McLean & Tobin, 1987)
Isothermal calorimeters are sealed chambers, where surfaces are lined with a barrier layer of insulating material and surrounded by a constant temperature water layer. Sensible heat loss passes through the insulating barrier into the water layer causing a rise in temperature. Heat loss is measured via the temperature gradient across the barrier layer. Evaporative heat loss is estimated by measuring the increase in air humidity in the ventilating air.

The insulating barrier in original isothermal calorimeters was a closed air gap. Measurement of changes in either the volume or pressure of the air was used to estimate change in mean temperature. In 1949, Benzinger and Kitzinger introduced the gradient layer calorimeter (Benzinger, et al, 1958). The barrier layer in the gradient layer calorimeter is made up of a network of thermocouples spaced at regular intervals. Heat flow is proportional to the mean temperature gradient across the entire layer irrespective of location of the heat source within the cavity or size or shape of the cavity (Benzinger, et al, 1958).

Traditionally isothermic direct calorimeters were limited in size, with an internal volume of approximately 5m$^3$. More modern calorimeters have a volume of about 30m$^3$, which allows room for a bed, washbasin and toilet facilities (Murgatroyd & James, 1980). Even in the modern calorimeters, the size of the room is restricted, and as such spontaneous activity is limited thereby creating an artificial living situation, different from free-living environment.

The size of the direct calorimeters results in a relatively long response time for measurements (Jequier, 1980, Murgatroyd & James, 1980). Furnishings also affect evaporative heat losses (for example, perspiration in bedding), thereby increasing response time for measurement. Sensible heat losses other than those from the individual may also be introduced, for example heat from lights, television, warm drink or hot water from washing or showers (Murgatroyd & James, 1980). Gradient layer calorimeters are usually restricted in size (less than 2m$^3$) and therefore have a more rapid response time (Pittet, 1980). The restricted size of the calorimeter however limits measurement times to periods of less than six hours.

Heat-sink calorimeters do not measure heat transfer through surfaces. Instead heat is removed from the chamber via a liquid-cooled heat exchanger, which is regulated to ensure constant temperature of air entering and leaving the chamber. Evaporative
heat loss is measured by similar means to isothermal calorimeters, via change in air humidity.

The water-cooled garment is a form of heat-sink calorimeter, which comprises a suit worn next to the skin covering the hands, arms, legs, tops of the feet, torso and head except the face (Webb, et al, 1972). Water flows through the garment, which is constructed of plastic tubing. Insulating clothing layers are worn outside the garment, which eliminate contact with external air and which are permeable to water vapour (Webb, et al, 1972). Rate of heat removal by water circulation is controlled so as to maintain thermal comfort and reduce sweating (McLean & Tobin, 1987, p.171). Sensible heat loss is measured by change in water temperature. Evaporative heat loss is estimated from hourly measurements of the subjects’ weight, to 5 grams. The garment permits natural movements, allowing the subject to exercise, eat and sleep while measuring heat loss.

Using well-designed and calibrated equipment, carefully controlled techniques and appropriate duration of measurements, direct calorimetry can accurately measure heat exchange. Direct calorimeters however are expensive, require sophisticated equipment, trained technicians and are not practical in the clinical setting.

4.3 Indirect Calorimetry

Indirect calorimetry is a measure of oxidation of fuel based on respiratory gas exchange (Seale, et al, 1990, Webb, 1981). That is, it measures the amount of oxygen consumed (VO₂) and carbon dioxide produced (VCO₂). Measurement of energy expenditure by indirect calorimetry uses respiratory gas exchange to assess cellular metabolism and hence heat production (Figure 4.1).

Twenty-four hour measurements by indirect calorimetry have a number of advantages over direct calorimetry. Indirect calorimetry has a short response time allowing for measurement of the time course of energy expenditure over the 24-hour period (Jequier, 1980). In addition, respiration chambers (see Section 4.3.5, page 98) used for 24-hour indirect calorimetry measurements can be larger in size, permitting a more natural setting that allows for spontaneous activity, and are cheaper than direct calorimeters. Measurement of VO₂ and VCO₂ allows for the
calculation of the respiratory quotient (RQ), which is not available with direct calorimetry.

RQ is the ratio of carbon dioxide production (VCO₂) to oxygen consumption (VO₂):

\[
RQ = \frac{VCO_2}{VO_2}
\]


<table>
<thead>
<tr>
<th>Substrate</th>
<th>RQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbohydrate</td>
<td>1.0</td>
</tr>
<tr>
<td>Protein</td>
<td>0.8</td>
</tr>
<tr>
<td>Fat</td>
<td>0.7</td>
</tr>
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4.3.1 Assumptions and Limitations

Assumptions that underlie indirect calorimetry measurements include:

- All oxygen and carbon dioxide exchange occurs across the lung;
- Oxygen and carbon dioxide are not stored within the body;
- All oxygen consumption and carbon dioxide production are associated with ATP synthesis (Ferrannini, 1988, Frankenfield, 1998).

Based on these assumptions, a number of limitations apply. Indirect calorimetry measures the amount of oxygen consumed and carbon dioxide produced associated with oxidation of substrates. Oxidation of protein however, is not complete, with some oxygen and carbon combining with nitrogen to produce urea, which is excreted in urine (Frankenfield, 1998, Groff, et al, 1995, p.468, Simonson & DeFronzo, 1990). For every 1g of nitrogen excreted, approximately 6L of oxygen are consumed and 4.8L of carbon dioxide are produced (Groff, et al, 1995, p.468, Wilmore, 1977).

Oxygen and carbon dioxide can also be involved in processes not associated with ATP synthesis, such as acid-base disturbances, hyper- or hypoventilation, or free radical production. Indirect calorimetry cannot distinguish between oxygen
consumption involved with ATP synthesis and that which is not (Frankenfield, 1998). In normal healthy people under physiological conditions the amount of oxygen consumption and carbon dioxide production that is not associated with ATP production is likely to be negligible.

The body stores very little oxygen due to the limited reserve pool. As such, oxygen consumption at the mouth very quickly reflects oxygen consumption at the cellular level. In contrast, carbon dioxide produced by cells enters a large bicarbonate pool, resulting in a time delay between changes in metabolic production of CO₂ and expired CO₂ concentration (Ferrannini, 1988).

4.3.2 Converting Respiratory Gas Exchange to Energy Expenditure

Traditional methods for deriving energy expenditure from gas exchange data were complex and involved measurement of urinary nitrogen excretion and calculation of non-protein RQ. In 1949, Weir (1949) developed a more simplified equation:

\[
EE = VO_2 (3.941) + VCO_2 (1.106) – UUN (2.17) \quad \text{Equation 2}
\]

Where: 
- \( EE \)  = energy expenditure, in kcal/d;
- \( VO_2 \)  = oxygen consumption, in L/d
- \( VCO_2 \)  = carbon dioxide production, in L/d;
- \( UUN \)  = urinary urea nitrogen, in g/d

Correct conversion of gas exchange data into energy expenditure requires measurement of urinary urea nitrogen (UUN) to correct for incomplete oxidation of protein. Weir (1949) noted however, that ignoring the protein correction produced a negligible error of 1%, for every 12.3% of total energy intake from protein. The typical contribution of protein to total energy intake in Western populations, ranges from 10 – 15% (Westerterp, 1993), however is likely to have increased over the last 10 years due to increasing popularity of high protein diets.

As the effect of incomplete protein metabolism on energy expenditure is negligible a simplified abbreviated Weir equation is often used, due to difficulties associated with collecting urine samples.

\[
EE \ (\text{kcal/d}) = VO_2 (3.94) + VCO_2 (1.11) \quad \text{Equation 3}
\]
Other investigators have also found small differences (<2%) in energy expenditure when correction for nitrogen excretion is not included (Bursztein, et al, 1989).

4.3.3 Closed Circuit and Open Circuit Systems

Indirect calorimetry systems may either be closed circuit or open circuit. With closed circuit systems subjects breathe from a reservoir of 100% oxygen (Matarese, 1997). VO$_2$ is then calculated from the decrease in oxygen volume over time. The disadvantage with closed systems is that the work of breathing may be increased, particularly in mechanically ventilated patients (Branson, 1990).

In open-circuit systems subjects breathe room air (or air from a ventilator) and expired air is collected in a sampling system before being released back into room air (Matarese, 1997, Simonson & DeFronzo, 1990). In contrast to closed circuit systems, open circuit systems using the same collection system do not affect the work of breathing (Branson, 1990, Matarese, 1997). Air enters via an inlet and is drawn through the system by negative pressure created by a pump located at the outlet of the system (McLean & Tobin, 1987, p.95). Leakage of expired air into the atmosphere is minimised by the negative pressure forcing expired air out of the system to be sampled.

The main disadvantage with most open circuit systems is that they require the calculation of inspired minute ventilation (the volume of air inspired per minute), which is necessary to determine VO$_2$ and VCO$_2$, as the volume of air inspired is not directly measured (Frankenfield, 1998, Matarese, 1997, Simonson & DeFronzo, 1990). The Haldane equation is used to calculate inspired minute volume from expired volume and concentrations of inspired oxygen and expired oxygen and carbon dioxide, assuming that nitrogen concentration is constant in both inspired and expired gases (Branson, 1990). Errors in the calculation of inspired minute volume are introduced at high levels of inspired oxygen concentration (upper limit of 60%), as might occur with mechanically ventilated patients (Frankenfield, 1998, Matarese, 1997, Simonson & DeFronzo, 1990). Indirect calorimetry measurements using portable collection systems cannot usually be conducted in patients with chest tubes or tracheostomies due to air leaks (Branson, 1990).

4.3.4 Comparison with Direct Calorimetry

Studies of simultaneous measurements of energy expenditure by direct calorimetry (by gradient layer or water cooled garment) and indirect calorimetry (by respiration

Webb et al (1980) cite work by Burton in 1935 and Hardy, Milhorat and DuBois in 1938, indicating less accuracy between simultaneous direct calorimetry and indirect calorimetry measurements when conducted over shorter periods of 3-6 hours. Discrepancy is likely to be apparent between these two measurements when conducted for periods of less than 24 hours due to heat storage (see Section 4.2, page 92). A study by Webb et al (1980) showed that the difference between energy expenditure measured by indirect calorimetry and that measured by direct calorimetry increased as work and activity increased and when food intake was less than expenditure.

Providing correct calibration, gas analysis, measurement of airflow and carefully controlled techniques, indirect calorimetry is considered a valid method for measuring energy expenditure.

4.3.5 Traditional Indirect Calorimetry Techniques
Several instruments have been developed using indirect calorimetry. Energy expenditure may be measured over periods of 24 hours or more, or may be limited to shorter periods (1 to 8 hours) to measure components of energy expenditure (BMR or REE).

Respiration Chamber
Measurement of energy expenditure over 24 hours or more using classical indirect calorimetry requires a respiration chamber. A respiration chamber is an airtight room that is ventilated with fresh air. The room is usually large enough to contain a bed, chair and table, toilet and sometimes a treadmill for exercise (Webb, 1991). Airflow rate and the difference between inlet and outlet concentration of oxygen and carbon dioxide are continuously measured. Energy expenditure due to physical activity can also be measured in the chamber using a radar receiver based on the Doppler principle (Jequier & Schutz, 1983). Use of the respiration chamber for measuring energy expenditure in the clinical setting however, is not practical or feasible.

Twenty-four hour measurements of energy expenditure in respiration chambers are also impractical. As such, more portable indirect calorimetry techniques have been
developed that allow for measurement of energy expenditure over shorter time periods. These techniques use different collection systems for expired air – bag systems, ventilated hood (canopy), facemask or mouthpiece plus noseclip. The portable collection systems offer the advantage over the respiration chamber of shorter response times and access to subjects (eg for blood sampling, measurement of blood pressure etc) (Jequier, 1980, Webb, 1991).

**Douglas Bag**

The most common bag collection system is the Douglas Bag. Douglas bags are lightweight canvas bags, lined with rubber, and are available in several sizes. A large rubber hose connects the top of the bag to a three-way tap, which is connected by tubing to a respiratory valve system and mouthpiece (McLean & Tobin, 1987, p.79). A noseclip is also applied to ensure collection of all expired air via the mouth. All expired air is collected in the bag. The collection time may be for a fixed time period or until the bag is filled, and the time recorded (McLean & Tobin, 1987, p.79). The contents of the bag are passed through a gasmeter and expired air is analysed for volume and gas concentration.

The Douglas bag can be attached to the subjects back using shoulder straps, allowing measurement of energy expenditure during a range of activities not possible with respiration chambers (McLean & Tobin, 1987, p.78). Sources of error with this collection system include leaks from the bag and diffusion of gas. Leaks in the bag may develop particularly with prolonged use. Prior to measurements, the bag should be tested for leaks. The material of the bag, particularly rubber is permeable to gases and as such gases such as CO₂ may diffuse from the bag. A comparison of different storage systems indicated that plastic bags permit a lesser amount of diffusion of CO₂ than rubber bags over a 24-hour storage period (McLean & Tobin, 1987, p.81). If gas analysis is conducted relatively quickly following collection (10-15 minutes) error introduced by diffusion of gas is negligible (McLean & Tobin, 1987, p.82).

**Ventilated Hood, Face-Mask, Mouthpiece plus Noseclip**

The ventilated hood is a plastic, Perspex or polythene canopy that covers the head or upper part of the body, allowing the subject to breathe freely (McLean & Tobin, 1987, p.95). The canopy is ventilated by a continuous influx of atmospheric air via an inlet in the system. Air entering the hood can be drawn from fresh air outside of the building to avoid mixing with expired air from the investigator (Jequier, 1980).
The ventilated hood can be used in subjects for 4 to 8 hours with minimal discomfort and with minimal air leaks from the system. Although the ventilated hood is less intrusive, some people have found it to be claustrophobic (Segal, 1987).

Other portable systems utilise a facemask or a mouthpiece plus noseclip. Both of these collection systems however can only be used for short periods of time, since it is almost impossible to avoid air leaks and may cause discomfort for the subject (Jequier, 1980, Simonson & DeFronzo, 1990). It is difficult when using facemasks to form a tight seal around the mouth and nose to avoid leakage of expired air (for example, subjects with facial hair). Mouthpieces may cause difficulties for subjects when swallowing.

Weissman et al (1984) studied healthy subjects and post-operative patients and found that minute ventilation was increased by 20 to 25% for the group when a standard mouthpiece (17mm diameter) plus noseclip were used compared to ventilated hood. Increases in minute ventilation were due primarily to increases in tidal volume (volume of breath) as breathing frequency (breaths per minute) was not altered (Weissman, et al, 1984). Based on the data presented by the authors, it is not possible to determine what influence this has on measured energy expenditure. McLean and Tobin (1987, p.96) however suggest that the effects on breathing would not greatly influence energy expenditure. In the same study however, Weissman et al (1984) investigated the effect of a mouthpiece of a smaller diameter (9mm) on respiration. Use of the smaller mouthpiece plus noseclip did not significantly alter minute ventilation or tidal volume (Weissman, et al, 1984). Simonson and DeFronzo (1990) also note that untrained subjects breathing through a mouthpiece tend to involuntarily hyperventilate. Appropriate training of subjects to the equipment can assist in avoiding this.

Segal (1987) has shown that when subjects were familiarised with the different equipment, measurements of VO₂ and energy expenditure did not differ between the ventilated hood, facemask or mouthpiece plus noseclip (less than 2% difference for group means), although the duration of measurement differed with the ventilated hood compared to the facemask and mouthpiece plus noseclip. Soares et al (1989) similarly compared BMR measurements from an indirect calorimeter utilising a mouthpiece plus noseclip with a ventilated hood in six subjects. Their study showed a mean difference of -3.1% between mouthpiece plus noseclip and ventilated hood, indicating that for individuals the mouthpiece plus noseclip may measure BMR as
much as 8% below, up to 2% above BMR measured by the ventilated hood (Soares, et al, 1989). Forse (1993) compared VO\textsubscript{2}, VCO\textsubscript{2}, RQ and REE measurements between the different collection systems and found an 8.8% and 7.2% higher REE when the mouthpiece and facemask were used, respectively, compared to the ventilated hood. None of these studies however have appropriately compared agreement between the measurement methods using the recommended approach by Bland and Altman (1986).

### 4.3.6 New Indirect Calorimetry Devices

The Douglas Bag, ventilated hood, facemask and mouthpiece plus noseclip are classified as portable indirect calorimetry collection systems. These systems however are not easily portable, often requiring transportation with a large trolley containing the indirect calorimeter (gas analysers and collection system) and computer for storage of the data. The inability to easily transport these indirect calorimeters from patient to patient and their considerable expense prohibits their use in many clinical settings.

More practical, easily portable indirect calorimetry devices, which are relatively inexpensive, have been developed in recent years. To the investigator’s knowledge, two such portable devices were available at the time of the review.

**Cosmed K4 b\textsuperscript{2}**

The Cosmed K4 b\textsuperscript{2} (Cosmed Srl, Italy) is a portable telemetry system that measures oxygen consumption, carbon dioxide production, air flow and heart rate (Littlewood, 2002). Although the Cosmed K4 b\textsuperscript{2} is commonly used to measure energy expenditure during activities, there is little evidence regarding its accuracy for measuring energy expenditure at rest. The device uses a facemask for collection of expired air. Oxygen consumption and carbon dioxide production are converted to energy expenditure via the Weir equation (1949). Littlewood et al (2002) compared measurements of REE from the Cosmed K4 b\textsuperscript{2} with the Deltatrac II ™ metabolic cart (an open circuit ventilated hood indirect calorimeter). Their results indicated that the Cosmed K4 b\textsuperscript{2} might not be a valid device for measuring REE in adults – mean bias 1120 kJ (17%), limits of agreement -1820 to 4060kJ (-27% to 61%) (Littlewood, 2002).
**MedGem™**
The MedGem™ (HealtheTech Inc, Golden, CO, USA) is a portable indirect calorimeter that measures respiratory airflow and oxygen consumption (Figure 4.2). The MedGem does not measure carbon dioxide production, however it assumes a constant respiratory quotient (RQ) of 0.85 to determine REE (HealtheTech, 2002). Relative to the Cosmed K4 b², the hand-held MedGem is a more easily portable and practical indirect calorimetry device.

**Figure 4.3**: The MedGem™ portable indirect calorimeter (shown with facemask attached)

Calculation of energy expenditure from gas exchange is primarily based on oxygen consumption (Weir, 1949). The manufacturers have indicated that use of a constant RQ of 0.85 will result in a maximum error of ± 2.3% if actual RQ fluctuates within the range of 0.75 to 0.95 (HealtheTech, 2002). Other authors have supported calculation of energy expenditure from oxygen consumption alone (Brandi, et al, 1997). An RQ of 0.85 approximates the RQ in the post-absorptive state. Harris and Benedict (1919) in their well-known studies, note that when either oxygen or carbon dioxide determination were missing, an RQ of 0.85 was assumed. Using only oxygen consumption (mL/min), the MedGem calculates REE based on an amended version of the Weir equation (Weir, 1949) and adjusting for urinary nitrogen excretion assuming a dietary intake of 16% of energy from protein:

\[
\text{EE (kcal/d)} = 6.931 \times \text{VO}_2 \text{ (mL/min)}
\]

Equation 4

Prior to each measurement with the MedGem the device self-calibrates. During this period (approximately 5 seconds) the flow sensors, which measure relative humidity, temperature and barometric pressure, are set. The calibration period does not include testing of the oxygen analyser.
The indirect calorimeter uses a facemask or mouthpiece plus noseclip as the collection system. The MedGem self-determines when steady state has been achieved based on a proprietary algorithm (O Murphy, personal communication, HealtheTech Inc, USA, 22 September 2003). The algorithm discards data from the first two minutes of the test, after which a rolling boxcar methodology is used on reiterative sets of 30 breaths to determine the slope of the line of best fit for these successive samples. The test is terminated when steady state based on the minimal slope criterion (not defined) is achieved or after 10 minutes if steady state is not achieved. In this case, data during the last eight minutes of the test are averaged to provide an estimate of REE.

Limited research is available on the MedGem™. Two studies (of which one presented in abstract form only) have compared measurements of REE from the BodyGem™ against the Douglas Bag or metabolic cart with ventilated hood in healthy adults (Melanson, et al, 2003, Nieman, et al, 2003). The BodyGem (HealtheTech Inc, Golden, CO, USA) is equivalent to the MedGem device with the exception that the BodyGem provides a reading of REE only while the MedGem provides a reading for both \( VO_2 \) and REE. The two devices also differ administratively, as the manufacturers sought Food and Drug Authority (FDA) approval for the MedGem to be classed as a medical device.

Nieman et al (2003) studied 63 adults on two separate occasions within a two-week period. At each session two measurements from the BodyGem and Douglas Bag were made in random order. Measurements were conducted in the late afternoon after 4 hours of fasting and 10 minutes rest, with subjects seated. Measurements lasted 12 minutes for both devices, with the last 10 minutes used for calculating REE. For this study, the BodyGem was programmed to conduct REE measurements using the same protocol as the Douglas Bag, that is, the BodyGem did not terminate measurements based on the proprietary algorithm, as would normally be the case.

Within-day reliability for oxygen consumption for the BodyGem was \( r = 0.97 \) for both testing days (Douglas Bag, \( r = 0.90 \) and 0.92) and between-day reliability for the BodyGem was \( r = 0.80 \) to 0.86 (Douglas Bag, \( r = 0.75 \) to 0.86) (Nieman, et al, 2003). Mean difference in REE (average of the four measurements) between the BodyGem and Douglas Bag was 30kJ (7kcal, <1%), with limits of agreement ranging from -1114 to 1128kJ (-266 to 270kcal, ± 16%) (Nieman, et al, 2003). There
was no significant correlation between mean REE of the two methods and their difference scores.

Melanson et al (2003) measured REE on two mornings using both the BodyGem and a ventilated hood indirect calorimeter (SM-2900). Measurements were conducted in the morning after a 12-hour fast. Different body positions were used for the two techniques. Between-trial reliability was high for both the BodyGem ($r = 0.92$) and SM-2900 ($r = 0.97$) (Melanson, et al, 2003). On both mornings REE measured by the BodyGem was significantly higher than the SM-2900 (mean difference = 326 kJ, 78kcal, 5.1%). Although the mean difference was greater in this study, the limits of agreement were much narrower (167 to 485kJ, 40 to 116kcal). That is, the BodyGem may overestimate REE by as little as 2.6% up to 7.6%, compared to the SM-2900.

To date, comparison of the new portable indirect calorimeter with validated and traditional methods have only been identified in healthy adults. Validation of the instrument in other populations is also necessary. If validated in chronically and acutely ill patients, the MedGem would be a practical method for measuring patients' REE in a clinical setting.

### 4.3.7 Conditions for Indirect Calorimetry Testing

**Basal versus Resting**

Traditional measurements of basal metabolic rate are measured under strict conditions. BMR is defined as the energy expenditure of an individual, 10 – 18 hours after the last meal, while the individual is lying quietly at rest in a thermoneutral environment, in the absence of physical or psychological stress (Berke, et al, 1992, Kinney, 1983). Measurement of energy expenditure under these strict conditions is not always possible. Traditionally, subjects were required to spend the night before testing at the research centre or hospital and measurements are conducted immediately upon wakening (Berke, et al, 1992, Feurer & Mullen, 1986). Measurement of BMR under these conditions is therefore expensive (cost of hospital bed, nursing staff time, night time meal etc), time consuming and inconvenient for both the subject and researcher (Turley, et al, 1993).
Measurement of REE is conducted under conditions that differ from the strict criteria for BMR measurement. There is considerable variation however in the conditions and protocols used for measuring REE.

**Pre-testing Conditions**
For measurements of REE subjects may spend the night before the measurement at the research centre or spend the night at home and travel to the centre early in the morning. A number of investigators have compared measurements of REE under these two conditions to determine whether it results in differences in measured energy expenditure. Two studies found that the place where subjects spend the night before the measurement had no effect on measured REE (0 – 2% difference between home and centre) (Fredrix, et al, 1990, Turley, et al, 1993). Berke et al (1992) however claimed that measurements conducted when the patient had spent the night at home were significantly higher (approximately 8%) than when the patient had spent the night at the centre.

This difference is likely to be explained by the fact that Berke et al (1992) were in fact comparing two different measurements of energy expenditure. Measurements conducted under “inpatient” conditions were in fact measurements of BMR; while measurements conducted under “outpatient” conditions more closely matched the protocol for measurement of REE. The results they found are consistent with other reports that energy expenditure measured under resting conditions is approximately 10% higher than basal conditions (Kinney, 1983, Matarrese, 1997, Turley, et al, 1993).

While most studies continue to measure REE in the post-absorptive state (10-12 hours fast), some studies have reduced the time period from the last meal, allowing for a light breakfast to be eaten or measured in the afternoon after lunch (Dempsey, et al, 1984, Feurer & Mullen, 1986). Fredrix et al (1990) compared differences in REE when measured after a standard 10-hour fast and when measured in the mid afternoon (three hours after lunch). Mean measured REE in the mid-afternoon was significantly higher (14%, p < 0.001), than REE measured in the early morning.

For measurements of REE, particularly when conducted under “outpatient” conditions, a resting period prior to the commencement of measurement is recommended to avoid the effect of previous activity (Battezzati & Vigano, 2001). Frankenfield (1998) recommends resting at least 15 minutes prior to the initiation of
measurements, while Feurer and Mullen (1986) recommend a rest period of greater than 30 minutes.

As long as pre-testing conditions used are consistent within a study, results should be internally valid. Problems may exist when comparing results between laboratories, where different methods may have been used or methods used are not made explicit.

**Calibration of Equipment**

Procedures for calibrating equipment differ with each device however all require calibration on a regular basis and prior to each measurement. Gas analysers are calibrated against reference gases of know concentration prior to each measurement (Matarese, 1997). The flow sensor is calibrated by repeatedly testing a known volume standard at different flow rates (Matarese, 1997).

Prior to calibration of equipment and measurements, it is essential that room temperature, barometric pressure and humidity be measured so that gas volumes can be corrected for dry standard temperature and pressure (0°C, 1atm) (Branson, 1990).

**Measurement Protocol – Length & Steady State Criteria**

There is variation in the measurement protocols and “steady state” criteria reported in the literature for conducting energy expenditure measurements (Table 4.2). As the portable indirect calorimetry devices are not suitable for 24-hour measurements, short-term measurements of REE have often been used. For tests to be considered accurate a stable measurement period should be achieved, to reduce error (Feurer & Mullen, 1986, Matarese, 1997, McClave, et al, 2003). A stable period of energy expenditure measurement (“steady state”) for short-term measurements will agree more closely with 24 hour measurements (McClave, et al, 1999, McClave, et al, 2003).
Table 4.2: Comparison of reported measurement protocols in the literature for measuring energy expenditure

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Length of Measurement</th>
<th>Data/Criteria used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long et al (1979)</td>
<td>4 – 5 hours</td>
<td>4 to 5 one hour measurements</td>
</tr>
<tr>
<td>Bernstein et al (1983)</td>
<td>Not defined</td>
<td>Not defined</td>
</tr>
<tr>
<td>Dempsey et al (1984)</td>
<td>Until criteria met</td>
<td>5 consecutive 1 min intervals where VO(_2) and VCO(_2) within ± 2%</td>
</tr>
<tr>
<td>Feurer et al (1984)</td>
<td>Until criteria met</td>
<td>5 consecutive 1 min intervals where VO(_2) and VCO(_2) within ± 5%</td>
</tr>
<tr>
<td>Bogardus et al (1986)</td>
<td>At least 50 mins</td>
<td>Mean of last 40 mins</td>
</tr>
<tr>
<td>Owen et al (1987, 1986)</td>
<td>10 mins</td>
<td>Mean of last 5-6mins</td>
</tr>
<tr>
<td>Ravussin et al (1986)</td>
<td>40 mins</td>
<td>20 – 25 mins adaptation; 9 – 15 mins analysed</td>
</tr>
<tr>
<td>Fearon et al (1988)</td>
<td>40 minutes</td>
<td>Not defined</td>
</tr>
<tr>
<td>Foster et al (1988)</td>
<td>Until criteria met</td>
<td>5 consecutive minute intervals, where CV for VO(_2) and VCO(_2) ≤ 5%</td>
</tr>
<tr>
<td>Lawrence (1988)</td>
<td>30 mins</td>
<td>Average of 3 x 10min periods</td>
</tr>
<tr>
<td>Henry et al (1990)</td>
<td>15 – 25 mins</td>
<td>Average of 3 x 6-8min periods (5 min rest between)</td>
</tr>
<tr>
<td>Mifflin et al (1990)</td>
<td>Until criteria met</td>
<td>3 mins of steady state; criteria not defined</td>
</tr>
<tr>
<td>Ireton-Jones &amp; Turner (1991)</td>
<td>Until criteria met</td>
<td>3 consecutive 1 minute intervals within 10% (does not specify what variables)</td>
</tr>
<tr>
<td>Ferraro et al (1992)</td>
<td>9 – 15 mins</td>
<td>Not defined</td>
</tr>
<tr>
<td>Arciero et al (1993)</td>
<td>45 mins</td>
<td>Not defined</td>
</tr>
<tr>
<td>Heshka et al (1993)</td>
<td>15 mins</td>
<td>Not defined</td>
</tr>
<tr>
<td>Falconer et al (1994)</td>
<td>20 mins</td>
<td>Not defined</td>
</tr>
<tr>
<td>Amato et al (1995)</td>
<td>&gt;15 – 30 mins</td>
<td>15 – 30 mins after steady state achieved; steady state not defined</td>
</tr>
<tr>
<td>Butte et al (1995)</td>
<td>40 mins</td>
<td>Not defined</td>
</tr>
<tr>
<td>Poehlman &amp; Toth</td>
<td>45 mins</td>
<td>Not defined</td>
</tr>
</tbody>
</table>
(1995)
Taaffe et al (1995) 15 mins Mean last 10 mins
Case et al (1997) Until criteria 3 or more consecutive 30-sec intervals
met where CV for VO₂ ≤ 10%
Klausen et al (1997) 60 mins Not defined
Sparti et al (1997) 30 mins Not defined
Coss-Bu et al (1998) Until criteria 15 – 20mins after steady state, where CV
met for VO₂ and VCO₂ 5-10% over 5mins
Piers et al (1998) 35 mins Mean last 15 mins
Ahmad et al (1999) Until criteria VO₂ and VCO₂ in steady state for 15-
met 20min; steady state not defined
White et al (2000) Until criteria 30 mins of steady state; criteria not
met defined
Bosaeus et al (2001) Not defined Not defined
Buchholz et al (2001) 60 mins Last 40mins averaged
Barak et al (2002) 30 mins, Last 20mins averaged
Heymsfield et al (2002) 40 – 60mins Stable measurement phase; criteria not
defined
Littlewood et al (2002) 20 mins Not defined
Nieman et al (2003) 12 mins Average of last 10mins
Siervo et al (2003) Until criteria RQ, VO₂, Vₑ stable for 5 mins, stability
met criteria not defined

VO₂: oxygen consumption; VCO₂: carbon dioxide production; CV: coefficient of variation;
RQ: respiratory quotient; Vₑ = minute ventilation

McClave et al (2003) define steady state interval as “a single 5 minute period during
which average minute oxygen consumption (VO₂), carbon dioxide production
(VCO₂) and respiratory quotient (RQ) change by less than a predetermined
percentage range”. Definitions for steady state vary within the literature (Table 4.2).
Some laboratories do not specify steady state criteria, instead selecting a
predetermined time interval, over which values are averaged. Many studies do not
specify or define the measurement protocols used.

McClave et al (2003) tested different measurement protocols (steady state periods
and time intervals) to determine the optimal criteria which best agreed with 24-hour
energy expenditure. Measurements were conducted on 22 haemodynamically
stable, mechanically ventilated patients for 24 hours. Seven snapshot protocols were compared – consecutive five minute steady state periods where VO₂ and VCO₂ change by \(\leq 10\%\); VO₂ and VCO₂ change by \(\leq 15\%\); VO₂ and VCO₂ change by \(\leq 20\%\); time intervals of initial 20 minutes; initial 30 minutes; initial 40 minutes; initial 60 minutes. The different protocols were compared to 24-hour energy expenditure by paired t-tests and primarily weighted by correlations. The highest correlation was observed with the strictest protocol - consecutive five minute steady state where VO₂ and VCO₂ change by \(\leq 10\%\) (McClave, et al, 2003). In patients with greater physiologic variation (high coefficient of variation for VO₂ > 9.0), higher correlations were observed between 24-hour energy expenditure and energy expenditure measured by the more strict criteria (change \(\leq 10\%\)) and longest interval (60 minutes), \(r=0.96\) and \(r=0.94\) respectively, compared to the other criteria (\(r = 0.73\) to 0.92) (McClave, et al, 2003). In patients with more stable VO₂, there was a smaller difference between the correlations for all protocols (\(r = 0.84\) to 0.94).

The need to achieve steady state during short-term measurements of energy expenditure is controversial. The results from the study by McClave et al (2003) however indicate that achieving a steady state by their criteria (\(\leq 10\%\)) is likely to assure a greater level of accuracy in the snapshot measurement of energy expenditure. Feurer and colleagues (1984, 1986) report using even stricter criteria – consecutive five minute steady state where VO₂ and VCO₂ change by \(\leq 5\%\).

Only one study listed in Table 4.2 (Foster, et al, 1988) reported a measurement protocol similar to that recommended by McClave et al (2003) or Feurer and Mullen (1986). Dempsey et al (1984) specified steady state criteria, allowing only for changes in VO₂ and VCO₂ of \(\leq 2\%\). Ireton-Jones and Turner (1991) and Mifflin et al (1990), report using three minutes of steady state data instead of five, however their criteria are not clearly defined.

Some investigators suggest that when steady state is not achieved, the data should not be used, as the validity of the measurement is questionable (Feurer & Mullen, 1986). Feurer and Mullen (1986) note from experience, that if steady state is not achieved within the first 15 minutes it is unlikely to be achieved at all. Frankenfield (1998) reports that energy expenditure measurements on lucid, spontaneously breathing patients will generally take longer than mechanically ventilated patients, due to awareness and the need to relax.
4.3.8 Physiological Ranges
Ensuring that measurements of VO2, VCO2 and RQ are within a physiological range can assess the accuracy of indirect calorimetry tests. Physiological values for VO2 and VCO2 are both within approximately 150 – 350 mL/min. For RQ, a well-documented physiological range of between 0.67 to 1.30 exists (Branson, 1990, McClave, et al, 2003). Indirect calorimetry measurements that produce values of RQ outside of this range may be due to some error in calibration, air leak in the system or experimental error (Branson, 1990, McClave, et al, 2003).

4.3.9 Reproducibility & Measurement Error
Any measurement instrument or tool should be assessed for the reliability or reproducibility of the measurement. Reproducibility of indirect calorimetry measurements may be determined by repeat measurements on the same day or between days, while carefully ensuring that conditions of the measurements are identical on repeat occasions. Wells and Fuller (1998) and Nieman et al (2003) have found high within-study and between-study reproducibility with traditional indirect calorimeters, Deltatrac Mk 1 Metabolic Monitor (within-study precision of <0.5%, between-study precision of <2%) and Douglas Bag (within-study precision of <0.1%, between study precision of <4%), respectively.


4.4 Doubly Labelled Water
The doubly labelled water (DLW) method measures carbon dioxide production and hence energy expenditure in a free-living environment. This method uses the difference between the elimination rates of two stable isotopes (H218O and 2H2O) to estimate carbon dioxide production rate (Davies, 1991, Seale, et al, 1990). An oral dose of the two isotopes is taken following collection of a pre-dose urine sample. Subsequent urine samples are collected over a period of one to three weeks. The method assumes that once consumed the hydrogen isotope (2H) equilibrates with total body water only and leaves the body only as water. The oxygen isotope (18O)
also equilibrates with total body water and leaves the body as water and in expired carbon dioxide. The difference in urine concentrations between $^2$H and $^{18}$O is equivalent to carbon dioxide production and can be calculated from the following equation (Davies, 1991):

\[
\text{CO}_2 \text{ production (L/d)} = \frac{(\text{No.ko} - \text{Nd.kd})}{2} \quad \text{Equation 5}
\]

Where:
- No = oxygen dilution space
- Nd = hydrogen dilution space
- ko = elimination rate of $^{18}$O
- kd = elimination rate of $^2$H

Inclusion of No and Nd in the equation accounts for exchange of the isotopes with non-aqueous hydrogen and oxygen in the body (Davies, 1991). This equation however must also be adjusted for isotopic fractionation of evaporative water losses, which is described in detail by Davies (1991).

The doubly labelled water method only measures carbon dioxide production and does not measure oxygen consumption. To calculate energy expenditure from equations such as the Weir equation (1949) an estimate of RQ over the study period is therefore required. If the RQ is not known and the subject is in energy balance the food quotient over the study period can be substituted (Black, et al, 1986).

Supply of $^{18}$O is limited globally and as such DLW measurements in subjects are restricted due to the large costs involved. In addition, measurement of energy expenditure by the doubly labelled water method in a clinical setting is neither practical nor feasible.

Measurement of energy expenditure is the most accurate method for determining energy requirements. In a clinical setting however measurement using direct calorimetry, traditional indirect calorimetry or doubly labelled water are rarely available or practical. Prediction equations, which most commonly estimate BMR or REE, are therefore often used in practice. To assess the accuracy of these methods against measurements of energy expenditure, techniques that measure REE instead of total energy expenditure should be used (i.e. traditional indirect calorimetry).
4.5 Analysis of Energy Expenditure Data

Following measurements of energy expenditure, data must be statistically analysed to address the hypotheses being tested. Energy expenditure data are frequently analysed inappropriately by incorrect adjustment for body size differences, which can distort the interpretation of the results. More recently, literature suggesting more appropriate methods for analysing data has been published (Bland & Altman, 1986, Davies & Cole, 2003, Toth, 2001). The following section provides a review of appropriate statistical methods for comparing energy expenditure measurements between groups, and for assessing agreement between methods.

4.5.1 Comparing Groups

Measured absolute REE (kJ/d) of two groups of differing body size cannot be directly compared. Energy expenditure data needs to be “normalized” or adjusted for differences in body size or composition (Carpenter, et al, 1995, Davies & Cole, 2003, Poehlman & Toth, 1995, Ravussin & Bogardus, 1989, Toth, 2001). Body composition (FFM) is usually used to “adjust” energy expenditure data, as it is the single best predictor of BMR and REE. The relationship between REE and FFM, for all possible values of FFM in mammals is curvilinear, with a zero y-intercept (Figure 4.3) (Wang, et al, 2000). Over the range of FFM values observed in normal adult humans (approximately 40 – 80kg) however, the relationship can be fitted with a linear function, with a non-zero y-intercept (Wang, et al, 2000).

Figure 4.4: Relationship between resting energy expenditure and fat free mass
(Adapted from Wang, et al, 2000)
The ratio method is commonly used to normalize REE, whereby REE (kJ/d) is divided by FFM (kg) or weight. The bias introduced by this method has been discussed in detail by other authors (Carpenter, et al, 1995, Davies & Cole, 2003, Heymsfield, 2002, Poehlman & Toth, 1995, Toth, 2001). In summary, applying the ratio method to REE data (REE = b[FFM]) assumes a zero y-intercept and does not completely remove the influence of FFM on REE. Davies and Cole (2003) show this using real data as an example.

FFM is not a homogenous body compartment. With increasing body weight and FFM there is a corresponding increase in the proportion of FFM as low metabolic rate tissues (skeletal muscle) and a decrease in the proportion as high metabolic rate tissues, such as the liver, brain and heart (Davies & Cole, 2003, Heymsfield, et al, 2002). Therefore, REE/kgFFM will decrease with increasing FFM.

Instead, a regression-based approach is recommended for comparing REE between groups of differing body size and composition. This approach adjusts REE for its linear relationship to FFM (REE = b[FFM] + c), assuming a non-zero y-intercept, thereby fully removing the effect of the normalizing variable. Regression lines can then be compared to determine whether there are clinical and statistical differences in the slopes or intercepts between the two groups (Davies & Cole, 2003). Adjusted means and standard errors can also be compared (Ravussin & Bogardus, 1989).

Assumptions with multiple linear regression analysis include normal distribution of both the dependent and independent variable, presence of a linear relationship, and homogeneity of variance in the dependent variable over all values of the independent variable (Tabachnick & Fidell, 2001, p.119, Toth, 2001).

Poehlman and Toth (1995) compared analysis of REE data by both the ratio method and regression-based approach to determine their impact on the interpretation of results. When REE data for males and females were compared, the ratio method indicated that females had a higher adjusted REE than males. In contrast, the regression based analysis resulted in a lower adjusted REE in females compared to males. Similar conflicting results were apparent when older and younger men were compared (Poehlman & Toth, 1995).
4.5.2 Comparing Methods

To compare different methods of measuring or predicting energy expenditure, the approach of Bland and Altman (1986) is recommended for assessing agreement between two measurement methods. This method is preferred to previous commonly used methods such as correlation coefficients, which assess the strength of the relationship and not agreement, and t-tests, which assess differences at the group level alone and do not consider discrepancies at the individual level.

The Bland and Altman (1986) method requires calculation of the mean bias (mean difference between the two measures) and limits of agreement (± 1.96 standard deviations of the bias). This method is best presented with the Bland-Altman plot, which plots the difference between the two measurements against the mean of the two measurements (Bland & Altman, 1986). The mean bias and limits of agreement are indicated on the plot. For good agreement between the two methods, the mean bias should be close to zero and the limits of agreement within a clinically acceptable range. The latter can also be assessed for any relationship between the measurement bias and true value (mean of two measurements) by means of correlation coefficient. If comparing a relatively new measure against a gold standard, the difference should still be plotted against the mean of the two measures and not against the gold standard, as this will produce misleading results. A plot against the gold standard will always show a correlation, whether this is true or not (Bland & Altman, 1995).

Recent studies have suggested calculating mean difference based on the absolute difference (positive integer) between individual measurements (Glynn, et al, 1999, Nieman, et al, 2003). The rationale behind this approach is that the positive and negative values cancel each other out resulting in a small mean bias and large range for the limits of agreement (Glynn, et al, 1999). By using only the absolute difference, the mean bias will be larger with narrower limits of agreement. Any assessment of agreement between two measurement methods for individuals must account for the limits of agreement. Therefore although the traditional approach may indicate a smaller mean bias the true level of agreement for individuals is also evident. The traditional method also allows for assessment of overestimation versus underestimation of methods, which is not apparent if absolute values are used in the analysis.
4.6 Cancer-Induced Weight Loss

Weight loss and malnutrition commonly occur in patients with cancer, the degree of which differs across different tumour types and stages. Approximately 20% of patients with cancer will die from the effects of malnutrition rather than the cancer itself (Ottery, 1994). The causes of weight loss and malnutrition in cancer patients are multifactorial. Weight loss in cancer patients may be due to functional (physiological) effects, which reduce energy intake, side effects of treatment (neurological or physical) or due to metabolic alterations associated with the tumour.

Reversal of weight loss in malnourished cancer patients is difficult (Evans, et al, 1987). However maintenance of weight and the attenuation of weight loss have been shown to have beneficial effects in terms of increased survival, improved quality of life and nutritional status (Davidson, et al, 2004, Isenring, 2003). The key component aiding weight maintenance in these patients has been the provision of intensive nutrition support to encourage increased energy and protein intake. Knowledge of patients’ energy requirements is therefore necessary to ensure that intake is adequate.

4.7 Energy Expenditure in Cancer

While it is common belief that energy expenditure is increased in patients with cancer, studies to date have shown inconsistent results, as described below. Ideally, the best method for determining the effect of cancer on energy expenditure would be to measure energy expenditure in a person prior to tumour development and after tumour development, however this is clearly not feasible. Therefore, the most appropriate method is to compare measured REE in cancer patients with measured REE in healthy or “control” subjects. Measurements of energy expenditure in cancer patients are also often compared to predictions of energy expenditure, based on predictions for healthy individuals, to determine if metabolism is altered in cancer patients.

4.7.1 Comparison with Controls

While numerous studies have been conducted to compare measured energy expenditure of cancer patients with control subjects, many have failed to use statistical analyses appropriate to their study design and hence may have influenced
the correct interpretation of results (refer to Section 4.5.1, pages 112-113). Of the 22 studies reviewed, only six conducted appropriate statistical analysis of the data (Appendix C, Table C.1). However, even within these studies there were variations in the analyses conducted, and most also reported traditional inappropriate methods for comparing groups, such as kJl/kgBW/d. Control subjects used in these studies include healthy subjects or non-cancer patients.

Of the many studies that have not conducted the recommended statistical analysis, differences in FFM and weight between the comparison groups are evident, highlighting the inappropriateness of these methods. Many of these studies have shown inconsistent results when different comparisons are conducted on the same dataset. For example, Scott et al (2001) studied 12 lung cancer patients and 7 healthy subjects. Cancer patients were significantly older and had a lower body weight (mean difference of 10kg, clinically significant) and lower total body potassium (measure of body cell mass, BCM) than healthy subjects. The authors reported that REE was significantly lower in cancer patients compared to controls when expressed in absolute terms (kcal/d), was no different when expressed per kilogram body weight (kcal/kg body weight/d), however was significantly higher when expressed per unit BCM (kcal/BCM/d) (Scott, et al, 2001). Each of these analyses produces different interpretations of the results hence highlighting the importance of analysing energy expenditure data appropriately.

Lindmark et al (1984) found a statistically significant difference in the regression lines of a group of weight-losing cancer patients (heterogeneous tumour sites) and weight-losing patients without cancer. No slopes, intercepts or adjusted means however were reported to determine the clinical significance of this difference. Hansell et al (1986) found no statistically significant difference in the regression lines for cancer patients (heterogeneous tumour site, weight-losing and weight-stable) and non-cancer patients (weight-losing and weight-stable) but found a significant difference in regression lines when weight-losing patients (cancer and non-cancer) and weight-stable patients (cancer and non-cancer) were compared. Again, no slopes, intercepts or adjusted means are presented however visual appearance of the regression lines indicates likely clinical insignificance for comparison of cancer and non-cancer patients, and clinical significance for comparison of weight-losing and weight-stable patients. This result suggests that it is the weight-losing state and not the presence of a tumour that affects energy expenditure. The patients in this study received an intravenous infusion of a 5% dextrose solution for the 12 hours
prior to measurement of indirect calorimetry. These measurements were therefore not conducted under true fasting conditions, however since the conditions were similar for each of the comparison groups, the differences observed would still be valid.

Fredrix et al (1991) conducted similar analyses with weight-losing and weight-stable gastric and colorectal cancer patients and weight-losing and weight-stable patients with non-malignant gastrointestinal disease. These authors however found conflicting results to the study by Hansell et al (1986). Fredrix et al (1991) found no difference in regression lines when patients were compared by presence or absence of cancer or compared by weight-losing or weight-stable state. It is likely that patients in this study had a lower degree of body weight loss as weight losing group was defined as weight loss $\geq 5\%$ compared to $\geq 10\%$ in the study by Hansell et al (1986), which may account for the difference between these studies. FFM in this study was measured by bioelectrical impedance analysis (BIA) using a regression equation developed in healthy populations (refer to Section 4.8.1, page 121-122).

Only two studies focusing on single tumour sites have used the correct analysis. Both Staal-van den Brekel et al (1997) and Jatoi et al (2001) found significant increases in small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC) patients, and NSCLC patients alone, respectively, when compared to healthy control subjects (matched for gender, age and FFM or BMI). Staal-van den Brekel et al (1997) also found a significant increase in REE in SCLC patients compared to NSCLC patients. However in both these studies some cancer patients had lost significant amounts of body weight while control subjects were weight-stable, which may have distorted results if the weight-losing state has a significant effect on REE as suggested by Hansell et al (1986).

### 4.7.2 Comparison between Cancer Characteristics

Variation in the results of studies investigating energy expenditure in cancer patients may be due to differences with the cancer patient studied. A number of studies have used a heterogeneous group of cancer patients of different tumour types and stages, including some patients with metastases (Bosaeus, et al, 2001, Fredrix, et al, 1991, Hansell, et al, 1986, Knox, et al, 1983). These studies have found no difference in REE between tumour types (Bosaeus, et al, 2001, Hansell, et al, 1986) or tumour stage (Staal-van den Brekel, et al, 1997) (Appendix C, Table C.1 and Table C.2). No correlation with REE has been found for tumour size (Peacock, et al,

A number of studies have measured REE in patients pre- and post-operatively following removal of the tumour, with conflicting results. However the time period post-surgery, which is likely to have an impact on energy expenditure, differs between studies. REE measured in cancer patients, five days post-curate surgery was shown to normalise (i.e. to within 90-110% of predicted REE) whereas significantly higher REE was measured in patients post-palliative surgery compared to pre-surgery REE (Luketich, et al, 1990). Fredrix et al (1991) found no significant difference between REE measured in cancer patients pre-surgery and seven to eight days post-surgery with no complications, whereas Arbeit et al (1984) observed a significantly lower REE in cancer patients measured a minimum of 10 days post-operatively compared to pre-operative REE. Follow-up of cancer patients approximately five months post-surgery showed no significant difference in REE compared to pre-surgery (Hansell, et al, 1986).

In these studies it is not always clear what analysis has been conducted for these comparisons, or even if the groups differ with respect to FFM or other measure of body size. It appears that most however have used inappropriate methods (eg ratio method) for analysing these data, and therefore these results should be interpreted with caution.

Falconer et al (1994) found an increased REE (kcal/kg body weight, kcal/kgFFM and kcal/kgBCM) in cancer patients with an acute phase protein reaction (c-reactive protein, CRP, >10mg/L) compared to cancer patients without. Although this analysis was using the ratio method, the authors reported that there was no significant difference in weight, FFM or BCM between the two groups.
4.7.3 Comparison with Prediction Standards


In four studies, measured REE was statistically and clinically significantly higher than predicted REE at the group level. Mean measured REE was 112 % (standard deviation, sd ± 14%) of predicted REE in a heterogeneous group of cancer patients, including both weight losing and weight stable patients (Bosaeus, et al, 2001). In patients with NSCLC mean measured REE was 118 (sd ± 12%) (Staal-van den Brekel, et al, 1995) and 116% (sd ± 14%) (Staal-van den Brekel, et al, 1997) of mean predicted REE. Patients with SCLC showed a higher percent of predicted REE than NSCLC patients at the group level, 124 (sd ± 14%) (Staal-van den Brekel, et al, 1997). Mean measured REE in weight losing lung cancer patients (SCLC and NSCLC) was higher than predicted REE (123 ± 12%) and higher than weight stable lung cancer patients (115 ± 13%) (Staal-van den Brekel, et al, 1994).

Measured REE, expressed as percentage of predicted REE, is often used to classify patients as hypermetabolic (> 110% of predicted REE), normometabolic (between 90-110% of predicted REE) or hypometabolic (< 90% of predicted REE). This ± 10% cut-off point for normal metabolism was originally defined based on the 95% confidence intervals for the Harris-Benedict equations (as well as the Schofield equations) for populations similar to those in which the equations were derived (young, lean individuals). Most studies have continued to use the ± 10% cut-off point for defining hypermetabolism and hypometabolism, although one study used a more liberal cut-off point of ± 15% to allow for greater variation in older, unwell populations (Fredrix, et al, 1991c).

Recommendations for increasing energy requirements for cancer patients would suggest that cancer patients would be classed as hypermetabolic. However, a number of studies have shown large variation in the degree of metabolism in cancer patients. Knox et al (1983) studied a group of 200 heterogenous cancer patients and
found that, when compared to predicted REE from the Harris-Benedict equations, the degree of metabolism varied, with 26% of patients classed as hypermetabolic, 41% classed as normometabolic and 33% classed as hypometabolic. Dempsey et al (1984) and Bosaeus et al (2001) observed similar results in 173 patients with cancer of the gastrointestinal tract (22% hypermetabolic, 42% normometabolic and 36% hypometabolic) and 297 patients with unselected cancer (48.5% hypermetabolic, 50.2% normometabolic and 1.4% hypometabolic), respectively. These variations in degree of metabolism may be due in part to the heterogenous nature of the groups in terms of tumour site and stage.

In a pilot study of pancreatic cancer patients, however, the same variation in degree of metabolism was observed – 20% hypermetabolic, 60% normometabolic and 20% hypometabolic (Bauer, et al, 2004). This result is particularly striking as most patients with pancreatic cancer often present with severe weight loss and cancer cachexia (DeWys, et al, 1980, Gorter, 1991).

More defined results were observed in studies of patients with lung cancer, with a greater proportion of patients classed as hypermetabolic when compared to Harris-Benedict predictions – 77% of NSCLC patients (Staal-van den Brekel, et al, 1995), 74% of both SCLC and NSCLC patients (Staal-van den Brekel, et al, 1994) and 67% NSCLC patients (Scott, et al, 2001).

While the Harris-Benedict equations are frequently used as the standards for “normal”, healthy people against which measurements of REE in ill people can be compared and hypermetabolism defined, several studies have shown that these equations are not appropriate for the current population and often overestimate requirements in healthy individuals (refer to Section 2.6, pages 21-40). Measured REE in control subjects, used for comparison with cancer patients, has also indicated overestimation of REE by Harris-Benedict prediction equations – 88% of predicted REE in weight stable healthy control subjects (Lindmark, et al, 1984); 85.8 and 90.2% of predicted REE in weight stable non-cancer patients and weight losing non-cancer patients, respectively (Hyltander, et al, 1991). Therefore, by using the Harris-Benedict equations as the standard for comparing measured REE in cancer patients, the number of true hypermetabolic patients is likely to be underestimated.
4.7.4 Predictive Accuracy of Equations

Most studies have used prediction equations as a standard for comparing measurements of REE in cancer patients but have not looked at the individual predictive accuracy of these equations. Individual predictive accuracy would support use of prediction equations as surrogate estimates of REE when measurements are not possible. Only one study of eight pancreatic cancer patients has used the approach of Bland and Altman (1986) to assess the agreement between measurement of REE and predicted REE from the Harris-Benedict equations as well as six other prediction methods (Bauer, et al, 2004). These authors also assessed the validity of using an injury factor of 1.3 with the Harris-Benedict equations as commonly recommended for practice (Curtin University of Technology, 1999, Roberts, 1997). Their results indicated that blanket application of such an injury factor was not appropriate with this group of patients due to their variation in the degree of metabolism.

4.7.5 Total Energy Expenditure

Despite inconsistent results in the literature, it is generally accepted that metabolic rate (hence REE) is increased in cancer patients. Regardless of the presence or absence of an increase in REE, patients with cancer, like other chronic diseases, experience a concomitant reduction in physical activity, that is often greater than any increases in metabolic rate, thereby resulting in a reduction in total daily energy expenditure (Gibney, 2000, McClave, et al, 1999, Toth, 1999, Toth & Poehlman, 2000).

4.8 Measurement of Body Composition

A brief review of methods for measuring body composition was also warranted due to the need for a measure of individuals' fat free mass (FFM) for analytical purposes. A number of methods are available for assessing FFM, some of which calculate FFM from measures of total body water (TBW). The most accurate methods for measuring FFM include hydrodensitometry, dual-energy x-ray absorptiometry, and deuterium dilution technique. These methods however are expensive and are not practical in the clinical setting. More practical, non-invasive and inexpensive methods have been developed.
4.8.1 Bioelectrical Impedance Analysis (BIA)

Bioelectrical impedance analysis (BIA) measures tissue conductivity by measuring the flow of an electric current through the body. The current is conducted through the electrolyte containing body water found in tissues such as muscle, bone and organs, while body fat impedes the conduction. The resistance to the flow of the electrical current is indirectly proportional to the volume of body water. This relationship is shown in Equation 6 (Hoffer, et al, 1969):

\[
\frac{\text{Volume}}{\text{Impedance}} = \frac{\text{Length}^2}{\text{Impedance}}\quad \text{Equation 6}
\]

In this equation length refers to the length of the conducting medium. In the case of measuring the volume of total body water in humans, height is used as the proxy for length and is directly proportional to the volume of body water.

Two types of BIA are available. The traditional tetra-polar surface electrode method requires subjects to lie flat and uses the voltage difference between distal (foot and hand) and proximal electrodes (ankle and wrist) to calculate resistance across the body (Ohm’s Law). More recently foot-to-foot BIA has been used, as it is more practical and duplicates as a weighing scale. The voltage difference is calculated from an electric current passed via electrode plates at the toes through to electrode plates on the heels. Based on measurements of TBW from impedance, FFM can be calculated assuming a constant hydration level of lean tissue of 73.2% (Hoffer, et al, 1969).

With measurements such as these there are always limitations. BIA assumes a constant hydration of FFM. However it is well known that the composition of FFM may be affected by various factors such as body position, hydration status, disease states and recent exercise, among others (Lukaski, 1996). In addition, the equations for calculating TBW from impedance are population specific and as such equations developed in healthy populations may not be appropriate for patients with diseases (Heymsfield, et al, 1996).

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(Tanita, Model TBF 305) in 57 healthy subjects (mean \(\pm\) standard deviation, age = 30 \(\pm\) 10 years). They found that BIA measurements of TBW were accurate for groups (mean bias of 0.7L) but decreased in accuracy at the individual level (\(\pm\) 2sd, 6.2L).

Jebb et al (2000) found a mean bias of 0.8kg (\(\pm\) 2sd, 7.9kg) fat mass when measured by foot-to-foot BIA (Tanita, Model TBF 305) using proprietary algorithm compared to a four-compartment model in 205 healthy subjects (age range, 16-78). Cable et al (2001) studied 192 healthy males (mean \(\pm\) sd age, 39 \(\pm\) 17 years) comparing FFM measured from foot-to-foot BIA (Tanita, Model TBF 105) with underwater weighing and observed a small mean bias of 0.07 \(\pm\) 3.5kg. In both these studies, accuracy of the foot-to-foot BIA was good for groups but was poor for individuals.

4.8.2 BIA in Cancer Patients

Only two studies have compared TBW measurements by foot-to-foot BIA with a gold standard (deuterium oxide dilution technique) in cancer patients. Isenring et al (2004) developed a regression equation based on TBW measurements (deuterium dilution technique) and impedance from foot-to-foot BIA (Tanita, Models TBF 410 and 300GS) in 27 patients with head and neck cancer receiving radiotherapy (mean \(\pm\) sd, age = 62 \(\pm\) 15 years). As with previous studies, these authors found that BIA measurements of TBW were accurate for groups but decreased in accuracy for individuals. Bauer (2003) compared 15 measurements of TBW by deuterium oxide dilution in seven patients with unresectable pancreatic cancer or non-small cell lung cancer, with measurements of TBW by foot-to-foot BIA using the equation of Isenring et al (2004). The Isenring et al equation was found to accurately predicted TBW for the group (mean bias 0.9 L) but the limits of agreement were wide for individuals (\(\pm\) 7.8 L) (Bauer, 2003).

4.9 Summary

Indirect calorimetry is an appropriate method for measuring REE via measurement of respiratory gas exchange. Traditional indirect calorimetry techniques are expensive, time consuming, required trained technicians to perform measurements and are not practical in the clinical setting. New indirect calorimetry techniques aim to provide a more easily portable and less expensive devices for measuring REE in

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the clinical setting (for example, at the patient’s bedside). For devices, such as the MedGem, to be acceptable for use in the clinical setting they need to be validated in patients with various diseases and injuries.

Appropriate methods for analysing energy expenditure data both for comparing groups and comparing methods, have been published (Bland & Altman, 1986, Davies & Cole, 2003). Studies measuring energy expenditure should adhere with these recommended analytical methods and not revert to inappropriate methods often used in the literature.

Weight loss and malnutrition are common in patients with cancer. It is common belief that cancer patients have altered metabolism and elevated energy requirements. Few studies have appropriately compared the REE of cancer patients with healthy controls. Those that have have shown inconsistent results. In situations where REE cannot be measured, use of prediction equations for estimating REE is warranted. Only one study has compared measured REE with REE predicted from various equations to determine the individual predictive accuracy of these methods in cancer patients. Most of these studies have been conducted on patients prior to commencing anti-cancer therapy and therefore do not necessarily provide direct clinical application, as most cancer patients requiring nutrition support are undergoing some form of anti-cancer therapy.
CHAPTER 5: REE IN CANCER (PHASE 2 METHODS)

CONTENT

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5.12 Manuscript 3 – Reducing the time period of steady state does not affect the accuracy of energy expenditure measurements by indirect calorimetry
5.1 Introduction

Weight loss and malnutrition are common in cancer patients (DeWys, et al, 1980), which may in part be a result of metabolic alterations caused by the tumour (Fearon, et al, 2001, Nelson, et al, 1994). As a result, it is commonly believed that energy expenditure and hence energy requirements are increased in cancer patients.

Recent studies have indicated that attenuating the weight-losing state and maintaining weight in cancer patients results in significant improvements in terms of quality of life, survival and nutritional status (Davidson, et al, 2004, Isenring, 2003). The ability to accurately determine the energy requirements of patients is vital to the provision of optimal nutrition support to ensure patients maintain weight.

Phase 1 of this research project (Chapter 3) indicated that there was error inherent in the use of traditional prediction methods for estimating the energy requirements of a cancer case study. Furthermore, dietitians' application of these methods, particularly injury factors, suggested a lack of understanding of the effect of cancer and its treatment on energy expenditure. Results of this phase warrant further investigation of more appropriate methods for determining patients' energy requirements in a clinical setting and a greater understanding of the energy expenditure of patients undergoing anti-cancer therapy.

While measurement of energy expenditure is the most accurate method for determining energy requirements, traditional measurement methods are expensive, time-consuming and impractical in the clinical setting. Alternative methods for determining energy requirements have therefore become popular. A new portable and practical device for measuring energy expenditure (MedGem™, HealtheTech, Golden, Co, USA) has not been validated for use in cancer patients. In addition, commonly used prediction equations have not been assessed for their individual predictive accuracy in cancer patients undergoing anti-cancer therapy.

The review of the literature also identified variations in the measurement methods used with traditional indirect calorimetry. Selection of steady state was one area where methods varied from study to study, which may impact on the accuracy of energy expenditure measurements. A measurement methods study investigating the accuracy of different steady state criteria was therefore warranted; the results of which would inform the remainder of the methods used in this Phase.
5.2 **Aims & Objectives**

This study was designed to address the two aims of Phase 2 of the research project. The objectives, with null hypotheses, are listed below. The objectives relate to the overall research project objectives (refer to Section 1.2, page 3)

**Aim:** To investigate differences in energy expenditure of cancer patients compared to healthy controls.

1. To compare measured resting energy expenditure (REE) of people with solid tumours to people without cancer.
   
   $H_{01} = $ There is no difference in the measured REE of people with solid tumours compared to people without cancer.

**Aim:** To compare different methods for determining energy requirements in people with cancer.

2. To investigate in people with solid tumours and in people without cancer the accuracy of a new, portable device for measuring energy expenditure compared to a validated method.

   $H_{02a} = $ There is no difference in the energy expenditure measured by the new device and the traditional method in people with solid tumours.

   $H_{02b} = $ There is no difference in the energy expenditure measured by the new device and the traditional method in people without cancer (healthy subjects).

3. To compare the individual agreement of actual measurements of resting energy expenditure with estimates from prediction equations in people with solid tumours and in people without cancer.

   $H_{03a} = $ There is no difference between measured REE and predicted REE in people with solid tumours.

   $H_{03b} = $ There is no difference between measured REE and predicted REE in people without cancer (healthy subjects).
4. To compare the individual agreement between measurements of REE using different steady state criteria.

H₀₄a = There is no difference in REE measured using five-minute steady state criteria and REE measured using four-minute steady state criteria.

H₀₄b = There is no difference in REE measured using five-minute steady state criteria and REE measured using three-minute steady state criteria.

Aim two included comparisons between methods in people without cancer to establish whether the healthy subjects recruited to the study and the study methods confirmed results found by other investigators. All hypotheses were tested using two-tailed comparisons, assuming no expectation of the direction of any discrepancy.

5.3 Study Design

These aims were considered in separate studies, the first in a case-control study, and the second using two clinical validation studies and a measurement methods study. All studies were cross-sectional. Repeated measurements were not conducted for both logistical (to minimise participant burden) and methodological reasons. Methodological reasons for not including repeated measurements in the study design were based on the hypotheses being addressed. That is, the hypotheses did not aim to demonstrate reproducibility of the individual measurement methods or assess intra-individual variation in energy expenditure. Reproducibility of the MedGem has previously been demonstrated (Nieman, et al, 2003, Wells & Fuller, 1998) and reproducibility of traditional indirect calorimetry has been discussed in Section 4.3.9 (page 110). Intra-individual variation for day-to-day differences in energy expenditure is well acknowledged to be in the order of 3-5% (Garby & Lammert, 1984, Henry, et al, 1989, Soares & Shetty, 1986).

Figure 5.1 provides a summary of the study design and identifies the hypotheses being tested (encircled numbers). The case-control study compared REE measured by traditional indirect calorimetry (VMax 229) between cancer patients (cases) and healthy subjects (controls). Cases and controls were group matched and not individually matched, with the intention that the fat free mass (FFM) of the two groups would be similar. Cases and controls were recruited over the same time frame however the sampling frame differed due to logistical reasons.
Figure 5.1: Study Design

Encircled numbers refer to hypothesis being tested (see text).
The clinical validation studies consisted of two comparisons each comparing to REE measured by traditional indirect calorimetry (VMax 229) in two different study populations. The cancer patients (cases) investigated in the case-control study were the same patients who participated in the clinical validation studies (hypothesis 2a and 3a). Likewise, the healthy subjects (controls) investigated in the case-control study also participated in the clinical validation studies (hypothesis 2b and 3b). The sampling frame, sampling procedure and recruitment procedure differed for the cancer patients and healthy subjects; however the data collection procedures were identical.

The measurement methods study was a side-study developed as a consequence of methodological gaps identified in the literature review (Chapter 4). This study compared different definitions of steady state for energy expenditure data collected from the traditional indirect calorimeter (VMax 229) for the combined sample of cancer patients and healthy subjects, after first determining whether there were differences in results based on health status. The results of this study informed the methods used in the remaining studies. As such, the results and discussion of this study are presented first at the end of this chapter (Manuscript 3).

5.4 Study Population

5.4.1 Cancer Patients
This thesis is focused on dietetic practice and therefore the target study population (cases) was patients whom dietitians would be likely to treat in a clinical setting, with particular reference to the weight-losing cancer state. Cancer itself is quite a broad diagnosis, consisting of various tumour types and sites. In terms of tumour type, both patients with solid tumours and haematological tumours generally require nutritional intervention. Significantly more literature however exists on the effect of solid tumours on energy expenditure, suggesting variable results (Appendix C, Table C.1). Studies on haematological tumours have primarily been undertaken in children. Compared to healthy control subjects, children with acute lymphoblastic leukaemia have shown no difference in REE either at diagnosis or during chemotherapy treatment (Bond, et al, 1992, Delbecque-Boussard, et al, 1997).

The study population was not restricted to one particular tumour site. This was primarily based on recruiting sufficient numbers but also with reference to the
ultimate generalisability of the results. Although data from patients all with one particular tumour would provide valuable information for that tumour site, results would be unlikely to be applicable to patients with other tumour sites. This was particularly relevant for hypothesis 2a of the study (comparison of new device with validated method). For this device to be of use in practice, validation for a wide range of patients was warranted. The validation study is based on assessing measurement error. To be considered valid in this population group measurement error should be small and constant irrespective of potential differences in the effect of different tumour sites on REE.

For the purpose of the study, which focused on patients requiring nutritional intervention, three tumour sites were excluded – breast, prostate and brain. These exclusions were based on firstly, the often lack of dietetic involvement in the treatment of these patients, as they are not usually weight-losing, and secondly due to the limited literature suggesting either no change in energy expenditure or reduced energy expenditure in these patients (Del Rio, et al, 2002, Demark-Wahnefried, et al, 1997, Demark-Wahnefried, et al, 2001, Kutynec, et al, 1999, Tayek, et al, 1990).

Finally, studies to date have generally excluded patients undergoing active treatment (radiotherapy, chemotherapy, surgery) for their cancer, and focused on the metabolic effect of the tumour itself. Once more, as this study focused on dietetic practice, the study population aimed to include patients, as they would generally present for nutritional intervention, which would encompass patients undergoing anti-cancer treatment (radiotherapy, chemotherapy, surgery).

5.4.2 Healthy Subjects
To compare with the REE of cases, control subjects were people without the disease. They were defined in this study as healthy subjects or people without cancer, which also excluded people with a history of cancer (eg in remission) regardless of the time period since the initial diagnosis.
5.5 Sampling Frame

5.5.1 Cancer Patients
New patients commencing treatment at the Wesley Cancer Care Centre (WCCC), a private radiation-oncology outpatient treatment centre in Brisbane, Australia, between July and December 2003, were used as the sampling frame for the recruitment of cancer patients.

As the WCCC is a private centre and hence patients tend to be on average of a higher socio-economic status the choice of this sampling frame may have introduced potential sampling error. The factors that are likely to influence energy expenditure however have previously been identified (refer to Section 2.3, pages 11-19), of which demographic factors such as socio-economic status are not included. The investigator therefore did not feel that this sampling frame would affect the representativeness of the sample in reflecting typical cancer patients in the context of this study.

Use of the radiation treatment centre as the sampling frame restricted the study population to patients with solid tumours and excluded patients with haematological tumours, as the latter group do not routinely receive radiation therapy. In addition, large numbers of patients with breast and prostate cancer receive treatment at the WCCC. If patients with these tumours were not excluded from the study, it is likely that the sample would have consisted predominantly of these patients. The sample of cancer patients would therefore have had a large representation of patients for whom nutrition intervention may not be relevant.

5.5.2 Healthy Subjects
A purposive sample was used for recruiting healthy subjects. Although ideal to recruit control subjects from the same population as the case subjects, this was not practical or possible. Other clinical validation studies of measured REE in cancer subjects recruited from a hospital have sometimes used non-cancer hospital patients as controls (Hansell, et al, 1986, Lindmark, et al, 1984, Nixon, et al, 1988). In this study, the sampling frame for cases was a radiation treatment centre and as such, the only patients attending this centre are cancer patients. If control subjects were recruited from the adjacent hospital, these patients would be inpatients.
whereas the cases are outpatients. Logistical and time-frame restrictions also prevented the investigator from using a more refined sampling frame.

In addition, as mentioned previously, FFM is the primary factor influencing a person’s REE and not other factors associated with their population or environment. Control subjects were group matched to the cancer patients based on age, weight and height and stratified by gender, to reflect the FFM of the group.

As the healthy subjects will be matched to cancer patients, the group of healthy subjects may represent a slightly older population, as cancer (particularly the types studied) tends to generally affect older persons. An attempt will be made to compare characteristics of healthy subjects with data of the general population in the similar age range, to determine the generalisability of our sample.

5.6 Sampling Procedures

5.6.1 Cancer Patients
The sample consisted of consecutive new patients attending the WCCC over a six-month period, who were assessed for eligibility. This six-month period appeared to be reflective of typical patients attending the WCCC.

**Inclusion Criteria**
Eligibility for cancer patients was based on the following inclusion criteria:
- Patient was male or non-pregnant, non-lactating female aged 18 years or over.
- Patient was diagnosed with solid tumour.
- Patient was ambulatory.
- Patient was willing to participate in the study and comply with study protocol after a) being fully informed about the study, b) reviewing the study methodology and c) providing written informed consent.

**Exclusion Criteria**
Cancer patients meeting the inclusion criteria were excluded based on the following criteria:
- Patients with solid tumours of the breast, prostate or brain.
- Patients who had undergone surgery within one month of the study.
• Patients with severe endocrine abnormalities, such as hyper- or hypothyroidism.
• Patients who were treated with high dose steroids (eg people with asthma).

These exclusion criteria were set as these conditions and treatments have independent effects on energy expenditure. Although this study tried to mimic clinical practice, in which cancer patients would be seen immediately post-operatively, surgery greatly increases REE however these increases are only short-term. The aim of this study however was to assess REE in cancer patients during the longer-term anti-cancer therapy (radiotherapy and chemotherapy) and not in the immediate post-operative period.

5.6.2 Healthy Subjects
Sampling of healthy subjects from the purposive sample was on a volunteer basis. Although voluntary involvement in a study introduces participant bias, in that people who volunteer are likely to be somewhat different from people who don’t volunteer, healthy subjects in this study were group matched to cancer patients on characteristics reflecting the FFM of the group and therefore attempted to limit the effect of its confounding in the study.

Inclusion Criteria
Healthy subjects were eligible for the study based on the following characteristics relative to the group of cancer patients, stratified by gender:
• People within ± 10 years of age
• People within ± 10cm height
• People within ± 5kg weight

This level of matching was considered to be close enough to reflect a clinically similar FFM between the cancer patient and healthy subject groups.

Exclusion Criteria
Healthy subjects matching the above characteristics were excluded based on the following criteria:
• People with a history of cancer.
• People who had undergone surgery within one month of the study.
• People with severe endocrine abnormalities, such as hyper- or hypothyroidism.
• People who were treated with high dose steroids (eg people with asthma).
5.7 Sample Size

Minimum sample sizes were calculated for addressing each hypothesis. Sample sizes were calculated using equations recommended by Kirkwood (1988).

5.7.1 Case-Control Study (Hypothesis 1)
Energy expenditure of cancer patients was compared to that of control subjects to determine whether there was a significant difference between the two groups (comparison of two means). Common recommendations are that cancer patients require 30% greater energy than healthy persons (Curtin University of Technology, 1999, Roberts, 1997). Based on previous studies, the standard deviation of mean REE for a group is approximately 10-15% (Siervo, et al, 2003, Staal-van den Brekel, et al, 1997, Taaffe, et al, 1995).

Assuming that a minimum relative difference in REE of clinical interest across comparison groups was 30%, then six subjects per group were required to detect this difference with 90% power and type I error of 5% or less (two-tailed). Allowing 20% for adjustment for confounding, a total of eight subjects per group needed to be recruited. This study aimed to recruit a total of eight cancer patients and eight control subjects.

5.7.2 Clinical Validation Study (Hypotheses 2a and 2b)
Two methods for measuring REE were compared to determine their level of agreement for individuals both in cancer patients and healthy subjects (comparison of paired means). Sample size calculations were similar irrespective of the study population. The coefficient of variation for intra-individual variation in BMR is 3-5% (Garby & Lammert, 1984, Henry, et al, 1989, Soares & Shetty, 1986). Accuracy of the two measurement methods was defined a priori as energy expenditure within 5% of validated methods, to account for intra-individual variation. Segal (1987) also based sample size calculations on a 5% difference between two measurement methods. The standard deviation of the difference was based on the results of the Nieman et al study (2003), which was 8%.

Allowing a minimum relative difference in REE between measurement methods of 5% to account for intra-individual variation, then 20 subjects were required to detect this difference with 90% power and type I error of 5% or less (two-tailed). As
comparison of these two measurement methods was conducted separately in both study populations, this study aimed to recruit a minimum of 20 cancer patients and 20 healthy subjects.

5.7.3 Clinical Validation Study (Hypotheses 3a and 3b)

Measured REE and predicted REE were compared to determine their level of agreement for individuals both in cancer patients and healthy subjects (comparison of paired means). As before, sample size calculations were similar irrespective of the study population. Prediction equations generally assume that measured REE will fall within ± 10% of predicted REE (Harris & Benedict, 1919). A minimum detectable difference of 10% was therefore used for this calculation. Previous studies have shown a standard deviation of the difference between measured and predicted REE of 10% (Siervo, et al, 2003, Taaffe, et al, 1995).

Assuming that a minimum relative difference of clinical interest between methods for determining REE is 10% and the standard deviation of measured REE is 10%, then a minimum of 11 subjects were required to detect this difference with 90% power and type I error of 5% or less (two-tailed). Allowing 20% extra for adjustment for confounding, a minimum total of 13 subjects was required. As comparison of measured and predicted REE will be conducted in both study populations, this study aimed to recruit 13 cancer patients and 13 healthy subjects.

5.7.4 Measurement Methods Study (Hypotheses 4a and 4b)

The minimum sample size required to test hypotheses 4a and 4b was calculated retrospectively. Refer to Manuscript 3 (Section 5.12, pages 149-164).

5.7.5 Final Sample Size

As all hypotheses were tested within the one study and one study population, the sample size was based on the largest minimum sample size calculated for the different studies. As such recruitment of subjects was aimed at achieving a sample size of 20 for both cancer patients and healthy subjects to provide sufficient power to detect differences of clinical significance with a minimal type I error for all hypotheses.

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5.8 Recruitment of Participants

5.8.1 Cancer Patients
Prior to recruitment of any patients, written and verbal approval from treating doctors and nursing staff at the WCCC was received. The WCCC nursing staff screened consecutive patients when they attended the centre for the planning of their treatment (approximately two weeks prior to commencement of treatment). Eligible patients were informed of the study and provided with an information package, including a consent form to provide contact details to the investigator (Appendix D). Nursing staff either posted the information package to eligible patients who were missed at the planning stage, or approached them once their treatment had commenced. Potential participants who were interested in the study signed the consent form and returned to nursing staff. The investigator received the signed forms from potential participants, after which they were contacted to further discuss the study and have any questions answered. Participants willing to participate in the study provided a written informed consent to participate in the study (Appendix D). Once consent was received participants were appointed a time for data collection. Involvement in the study was coordinated with their treatment at the centre, so as to minimise participant burden.

Nursing staff provided the investigator with de-identified demographic details (gender, age and tumour site) of eligible participants who declined to participate, or who were deemed inappropriate for the study, as decided by the nursing staff. Reasons for patients determined to be inappropriate for the study were recorded.

5.8.2 Healthy Subjects
Controls were primarily recruited through staff of the university via email and flyers. Family and friends of staff members were also targeted for involvement in the study. Details in emails and flyers provided the characteristics of male and female subjects that were necessary to be matched to cancer patients (Appendix D). Interested subjects with these characteristics contacted the investigator at which point subjects were assessed against the exclusion criteria and provided further information on the study if deemed eligible. Potential participants were posted or provided with an information package and provided written informed consent to participate in the study. Once consent was received participants were appointed a time for data collection.
The information packages and consent forms provided to cancer patients and healthy subjects were identical.

5.9 Ethics Approval

Ethical approval for the conduct of this study was received from the QUT University Human Research Ethics Committee (Ref No: 2723H) and The Wesley Hospital Multidisciplinary Ethics Committee (Ref No: 2002/13). Potential participants received an information package, provided by nursing staff, explaining in detail the purpose of the study and what it involved. Signed informed consent was received prior to commencement of any data collection.

Approval from the Therapeutic Goods Administration (TGA) was also required for use of the MedGem medical device as part of a clinical trial in Australia. The MedGem is currently not supplied for use in Australia. Approval for use of the device as part of the trial was granted (Ref No: 030/2003).

5.10 Data Collection Procedures

All data collection procedures were identical for cancer patients and control subjects, with the exception of collection of medical history data (Figure 5.1). The investigator collected all of the data on participants and recorded on data collection forms, which were colour-coded for cancer patients and healthy controls (Appendix E). It was not possible for the investigator to be blind to case-control status.

5.10.1 Pre-testing Conditions

All participants were provided with a list of instructions regarding what to do prior to data collection and details of the appointment. Participants were required to fast for 12 hours prior to commencement of data collection. Only water was allowed during this period. Participants were instructed to do minimal activity upon wakening in the morning and arrive at the hospital, within which the WCCC resides, at the specified time (between 7 and 8:30am). Once arriving at the hospital participants were greeted by the investigator and taken to a room where they rested quietly for at least 30 minutes. Participants were allowed to watch television during this time.
After the rest period, participants were taken to the laboratory, located nearby (approximately 10 metres) where the REE measurements were conducted. Although the effect of the rest period would be somewhat diminished, patients were seated and rested for a further 5-10 minutes prior to the commencement of energy expenditure measurement. Any effect introduced by moving patients would be the same between cancer patients and healthy subjects and would randomly affect REE measurements with the two indirect calorimeters. Hence while error is introduced there would be no bias in the comparison.

During both measurements of REE, participants sat in a reclinable chair and were asked to relax and remain as still as possible. Standard relaxation music was played in the background during both measurements. Measurements with the ventilated hood are usually conducted in a supine position. As both devices in this study used a mouthpiece and noseclip, measurements were conducted in a seated or semi-reclined position to avoid pooling of saliva in the mouth and difficulties swallowing, which is worsened when supine (Matarese, 1997).

### 5.10.2 VMax 229

The traditional indirect calorimetry device used for measuring REE was the VMax 229 (SensorMedics, Yorba Linda, CA, USA). This device utilises a mouthpiece plus noseclip (Figure 5.2). A mass flow sensor measured airflow and volume, which was calibrated prior to each measurement using a certified three-litre calibration syringe. Calibration was achieved when measured stroke volume was within ± 3% of syringe volume. Expired gas was analysed for oxygen concentration using a paramagnetic oxygen analyser and carbon dioxide concentration using a non-dispersive infrared analyser. Gas analysers were calibrated prior to each measurement using three known standard gas mixtures (16 ± 0.02% O₂, 4 ± 0.02% CO₂; 26 ± 0.02% O₂, 0% CO₂; room air 20.94% O₂, 0.05% CO₂). Calibration was complete when the gas analysers measured oxygen and carbon dioxide concentration within ± 5% of expected. The VMax 229 was set up for breath-by-breath analysis. Ambient room temperature ranged from 21 – 23 degrees Celsius.
Figure 5.2: Resting energy expenditure measured by the VMax 229 indirect calorimeter using a mouthpiece and noseclip

The indirect calorimeter was connected to an IBM compatible personal computer (Optiplex GX110, Dell, Malaysia) for management and storage of data using the VMax Vision software for Windows (Version 05.2A, SensorMedics, Yorba Linda, CA, USA). Respiratory quotient (RQ), defined as VCO₂/VO₂, was calculated by the software. VO₂ and VCO₂ were converted to REE using the abbreviated Weir equation (Weir, 1949):

\[
\text{REE} = \text{VO}_2 \times 3.94 + \text{VCO}_2 \times 1.11
\]

Where REE in kcal/d and VO₂ and VCO₂ in L/d

VO₂, VCO₂, RQ and REE were averaged for every 60-second period. Measurements were conducted until steady state was reached or for 30 minutes or until patients requested to cease measurements, whichever occurred first. Steady state was defined as three consecutive minutes during which the coefficient of variation for VO₂, VCO₂ RQ and minute ventilation (Vₑ) was ±10% (refer to Section 5.12, pages 149-164). If steady state criteria were not met, the data were not included in the subsequent analysis.

Two laboratory technicians performed the VMax 229 measurements. The investigator was present for all measurements and observed all methods undertaken. All steady state readings from the VMax Vision software were obtained by the investigator, ensuring consistency in this process.
5.10.3 MedGem

Measurements with the MedGem device used single-use disposable mouthpieces plus noseclip for collection of expired air (Figure 5.3). The MedGem device and disposables were supplied, gratis, to the investigator for use in the study by the distributors (SensorMedics, USA). All measurements with the MedGem were conducted by the investigator.

![Figure 5.3](image)

**Figure 5.3:** Resting energy expenditure measured by the MedGem™ indirect calorimeter using a mouthpiece and noseclip

Prior to commencing REE measurements, the device self-calibrates, a five second interval during which time the flow sensors measure relative humidity, temperature and barometric pressure. The oxygen analyser uses a dual-channel fluorescent quenching sensor, which is based on the deactivation of ruthenium in the presence of oxygen. The ruthenium cells are activated by an internal light source, which is quenched in the presence of oxygen (Nieman, et al, 2003). The amount of quenching is proportional to the oxygen concentration.

Termination of the measurements and identification of steady state is self-determined by the device. The MedGem uses a proprietary algorithm for the determination of steady state. The data during the first two minutes of a test are discarded and then a rolling boxcar methodology is used on reiterative sets of 30 breaths to determine the slope of the line of best fit for these successive samples (O Murphy, personal communications, HealtheTech Inc, USA, 22 September 2003). Steady state is declared and the test terminated when the minimal slope criterion is achieved, however these criteria have not been made explicit. When steady state is
not achieved a mathematical average of the data during the last 8 minutes of the test is used as the REE.

If an air leak is detected during the measurement the MedGem displays an error message and the measurement must be recommenced. When a successful measurement has been conducted the MedGem displays VO$_2$ (mL/min) and REE (kcal/d) on an LCD screen, however it does not identify whether steady state was achieved or an average of the data was taken. Measurements typically take 5-10 minutes. REE is calculated from VO$_2$ using a modified version of the Weir equation, where VCO$_2$ is equivalent to VO$_2$ x 0.85 and REE is adjusted for excreted urinary nitrogen assuming a dietary intake of 16% of energy from protein (HealtheTech, 2002):

\[
\text{REE (kcal/d) = 6.931 x VO}_2
\]

Where VO$_2$ is measured in mL/min.

As the traditional indirect calorimetry does not adjust for loss of energy due to urinary nitrogen excretion, this difference between the two indirect calorimeters will introduce a small degree of error in the order of approximately 1-2% (Weir, 1949). As such, REE was also estimated from measured VO$_2$ from the MedGem, without the adjustment for nitrogen excretion:

\[
\text{REE (kcal/d) = 7.029 x VO}_2
\]

Where VO$_2$ is measured in mL/min.

Measurements of energy expenditure with the two devices per individual were conducted in random order, established using a random number table.

### 5.10.4 Body Composition

Body composition was assessed by foot-to-foot BIA (Tanita Inc, Tokyo, Japan, Model 300GS) to limit burden on participants and for practical reasons. Measurements were conducted bare-footed and with heavy clothing removed. For healthy subjects the proprietary algorithm for calculating FFM was used. To calculate FFM for cancer patients, impedance measured by the foot-to-foot BIA was used to calculate TBW from the Isenring et al equation (2003):
TBW = 5.9 + 0.56 x Height^2 / Impedance

Where: TBW is measured in L, Height in cm, Impedance in Ω (ohms)

FFM was estimated from TBW assuming a hydration level of 73.2% (Hoffer, et al, 1969).

5.10.5 Predicted REE

REE was predicted from commonly used and more newly developed prediction equations. Predicted REE was calculated for both cancer patients and healthy controls. No prediction equations have been specifically developed for patients with cancer. All of the prediction equations used have been derived from healthy populations. Table 5.1 lists the seven prediction equations investigated in this study. For cancer patients, an injury factor of 1.3-1.5 is commonly recommended for use with the Harris-Benedict equations (Curtin University of Technology, 1999, Roberts, 1997). In addition to predicting REE from the Harris-Benedict equations (alone), for cancer patients REE was also predicted from the Harris-Benedict equations in combination with an injury factor, using the lower end of the recommended range (1.3). The units of energy calculated from the equations varied. Predicted REE values were calculated as per equation and then converted to kilojoules (kJ).

For participants with a BMI greater than 29kg/m^2, an adjusted weight was used in the calculation of REE from the Harris-Benedict equation. The adjusted weight was based on the recommendations from Glynn et al (1999) and Barak et al (2002). Adjusted weight was calculated as:

Adjusted weight (kg) = IBW + 50%(actual – IBW)

Where IBW is calculated from the Hamwi equation (1964).
Table 5.1: Prediction methods

<table>
<thead>
<tr>
<th>Equation</th>
<th>Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harris &amp; Benedict (1919)</td>
<td>( m ) BMR (kJ/d) = 278 + (57.5 \times W) + (20.9 \times H) – (28.3 \times A)</td>
</tr>
<tr>
<td></td>
<td>( f ) BMR (kJ/d) = 2741 + (40.0 \times W) + (7.7 \times H) – (19.6 \times A)</td>
</tr>
<tr>
<td>Schofield (1985)</td>
<td>( m ) BMR (MJ/d) = (0.048 \times W) + 3.653</td>
</tr>
<tr>
<td></td>
<td>( f ) BMR (MJ/d) = (0.034 \times W) + 3.538</td>
</tr>
<tr>
<td>Over 60 years</td>
<td>( m ) BMR (MJ/d) = (0.049 \times W) + 2.459</td>
</tr>
<tr>
<td></td>
<td>( f ) BMR (MJ/d) = (0.038 \times W) + 2.755</td>
</tr>
<tr>
<td>Owen et al (1987, 1986)</td>
<td>( m ) RMR (kcal/d) = 875 + (10.2 \times W)</td>
</tr>
<tr>
<td></td>
<td>( f ) RMR (kcal/d) = 795 + (7.18 \times W)</td>
</tr>
<tr>
<td>Mifflin et al (1990)</td>
<td>( m ) REE (kcal/d) = (10 \times W) + (6.25 \times H) – (5 \times A) + 5</td>
</tr>
<tr>
<td></td>
<td>( f ) REE (kcal/d) = (10 \times W) + (6.25 \times H) – (5 \times A) – 161</td>
</tr>
<tr>
<td>Cunningham (1991)</td>
<td>REE (kcal/d) = (21.6 \times FFM)</td>
</tr>
<tr>
<td>Wang et al (2000)</td>
<td>REE (kcal/d) = (21.5 \times FFM) + 407</td>
</tr>
<tr>
<td>20 kcal/kg (2002)</td>
<td>REE (kcal/d) = W x 20</td>
</tr>
</tbody>
</table>

BMR = basal metabolic rate; RMR = resting metabolic rate; REE = resting energy expenditure; \( m \) = male; \( f \) = female; \( W \) = weight (kg); \( H \) = height (cm); \( A \) = age (years); FFM = fat free mass (kg); kJ = kilojoules; MJ = megajoules; kcal = kilocalories

5.10.6 Nutritional Status

Nutritional status was measured using Subjective Global Assessment (SGA), which categorises people as well nourished (A), at risk of malnutrition or moderately malnourished (B), or severely malnourished (C) (Detsky, et al, 1987). Measurement of nutritional status was primarily used to describe the group of cancer patients. Healthy control subjects also had the nutritional status assessed for comparison with cancer patients.

5.10.7 Medical History

Medical history data was collected primarily for descriptive purposes. Where available information on tumour type and International Classification of Diseases (ICD) code, tumour stage, presence/absence of metastases, recurrence, treatment plan, general medical history and medications were collected. Tumour staging (tumour size, nodule involvement, metastases; TNM) was rarely recorded in the patients' medical records. Information on treatment plan included whether treatment
consisted of radiotherapy (XRT) and/or chemotherapy (CTx), whether XRT and/or CTx had commenced, ceased or current and whether the tumour had been resected or was planned to be resected. If patients had had surgery, details on whether the resection was complete or incomplete (positive margins) were recorded, where available.

5.10.8 Other Data
Additional data collected directly from participants included age, gender, weight, height, BMI, and weight history. The foot-to-foot BIA measured weight without heavy clothing or shoes to the nearest 0.1kg. Height was measured without shoes by stadiometer to the nearest 0.5cm (KaWe, Germany). These data were used for descriptive purposes and in order to determine whether or not it was possible to generalize our sample to the study population. These variables were also necessary for estimating energy requirements from prediction equations.

5.11 Statistical Analyses

Data were analysed using SPSS for Windows (version 11.0.1, 2001, SPSS Inc., Chicago, USA) statistical software package. Continuous variables are presented as mean ± standard deviation (unless otherwise stated) for Normally distributed variables or median (minimum – maximum) for variables not Normally distributed. Normality of continuous variables was assessed from visual interpretation of the mean, median, standard deviation, range, skewness, kurtosis and histogram (frequency distribution) for the individual variables. Categorical variables are presented as count (percentage). Significance was set at the conventional 95% limits (two tailed). All hypotheses were tested for both clinical importance and statistical significance.

5.11.1 Case Control Study (Hypothesis 1)
Characteristics of cancer patients and healthy control subjects were compared by independent sample t-tests (continuous variables) and Fisher’s Exact test (categorical variables). At the bivariate level, the association between health status and measured REE (VMax 229) was assessed by independent sample t-test. Based on the literature, it is well accepted that FFM is a confounder of this relationship. Normally, modelling for case-control studies would use logistic regression with health status as the outcome variable. However, although designed as a case-
control study, to answer the research question and address the hypothesis being tested, the association was reversed and multivariable linear regression analysis was used. For this model, measured REE was considered as the dependent variable, health status as the independent variable and FFM was included as a potential confounding variable.

A general linear modelling approach was taken for the regression analyses, which was used to adjust the association between measured REE and health status for differences in FFM between the two groups. Results were expressed as adjusted means ± standard errors.

Weight loss was also considered as a potential confounding variable however preliminary analysis indicated that weight loss was not associated with REE (adjusted for FFM) and therefore was not included in the final model. Tumour type and surgery were considered as potential effect modifying variables through stratified analyses; however small sample size precluded meaningful analyses.

5.11.2 Clinical Validation Study (Hypotheses 2a and 2b)

To address the hypothesis, the bias (discrepancy) between REE measured by VMax 229 and MedGem, was considered as the dependent variable in this analysis. The discrepancy was statistically tested against an expected zero difference if the two methods agreed. An acceptable difference of 5% was determined a priori.

Mean biases in REE and VO₂ measurements between the MedGem and VMax 229 were first assessed for any effect of order of administration of measurement by multiple regression analysis. There was no order or interaction (order x health status) effect for mean bias of REE or VO₂ between the two devices. Consequently analyses proceeded on pooled data ignoring order of administration.

Differences in the mean biases (MedGem – VMax 229) for measured REE and VO₂ between cancer patients and healthy subjects were assessed by independent sample t-tests. Although there was no statistically significant difference for REE or VO₂, the magnitude of the mean biases were of clinically significant concern, and as such data were analysed and presented separately for cancer patients and healthy subjects.
Mean biases between the two indirect calorimeters for measured REE and VO$_2$ were analysed for statistical significance by paired t-tests. Mean bias, limits of agreement ($\pm$ 2 standard deviations) and plot of bias against average of two measurements using the Bland-Altman approach (Bland & Altman, 1986) were used to describe agreement at the individual level and assess whether the bias was consistent across the entire range of measurements. Pearson’s correlation coefficients were used to assess whether there were trends in the magnitude of the bias with increasing REE and VO$_2$ measurements.

5.11.3 Clinical Validation Study (Hypotheses 3a and 3b)
Comparison of measured REE (by VMax 229) and predicted REE was conducted separately for cancer patients and healthy subjects. A clinically meaningful difference of 10% was determined \textit{a priori}.

Measured REE was compared to REE predicted by each prediction methods using the Bland-Altman approach (Bland & Altman, 1986). Paired t-tests were used to first assess agreement between the measured and predicted REE at the group level. Mean bias, limits of agreement ($\pm$ 2 standard deviations) and plot of bias against the average of measured and predicted REE were used to describe agreement at the individual level and assess whether the bias between predicted and measured REE was consistent across the entire range of REE measurements. Pearson’s correlation coefficients were used to assess whether there were any trends in the magnitude of the bias with increasing REE measurement.

5.11.4 Measurement Methods Study (Hypotheses 4a and 4b)
To address the hypothesis, biases between the steady state criteria (with five-minute criteria as referent) were considered as the dependent variable. A difference between steady state criteria of 2% was pre-determined to be of clinically significant concern.

Biases between the steady state criteria were not normally distributed. As such variables are presented as median (range or 2.5$^{th}$ to 97.5$^{th}$ percentile) and corresponding non-parametric tests were conducted. Characteristics of subjects who achieved five-minute steady state and those who did not were compared for both clinical importance and statistical significance by independent sample t-tests and Fisher’s Exact test.
Differences in measured REE between the three steady state criteria were first assessed by Wilcoxon signed rank tests. To compare our results with that of other studies, which cite correlation coefficients, Spearman’s rank correlation was used to determine the strength of the relationship of five-minute with four-minute steady state and with three-minute steady state criteria. Average bias, limits of agreement and plot of average difference against average of two measurements using the Bland-Altman plotting approach were used to describe agreement at the individual level and assess whether the bias was consistent across the entire range of measurements (1986). Spearman’s rank correlation was used to assess whether there was any trend in the bias with increasing REE measurements.

The data were initially analysed separately for cancer patients and healthy subjects to determine if the relationship differed based on disease status. There was no significant difference between cancer patients or healthy subjects for the average bias and limits of agreement, for both the comparison of five-minute and four-minute steady state data and five-minute and three-minute steady state data. As such, data presented are for the combined sample of cancer patients and healthy subjects.
5.12 Manuscript 3 – Reducing the time period of steady state does not affect the accuracy of energy expenditure measurements by indirect calorimetry

Citation:
Reeves MM, Davies PSW, Bauer J, Battistutta D. Reducing the time period of steady state does not affect the accuracy of energy expenditure measurements by indirect calorimetry. Journal of Applied Physiology, 2004; 97:130-134.

Date Submitted: November 2003

Date Accepted: March 2004

Contribution of Authors:
MMR was the main author of the manuscript, initiated and designed the study, carried out data collection, statistical analyses, interpretation and discussion of results. PSWD and DB assisted in design of the study, statistical analyses, interpretation and discussion of results and contributed to writing the manuscript. JB assisted in data collection and interpretation and discussion of results.

Please Note: The reference style for this manuscript is that appropriate for the journal.

The text of Manuscript 3 is not available online. Please consult the hardcopy thesis available from the QUT library
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Chapter 6: Results – REE in Cancer

6.1 Introduction

This chapter presents the results of Phase 2. The methods for this study have been described in Chapter 5. This chapter includes first a description of the sample in comparison to the study population to determine the generalisability of the results. The results of objectives 1, 2a, 2b and 3a have been presented in two manuscripts. Both manuscripts have been submitted for publication to international peer-reviewed journals. The manuscripts are followed by the results of objective 3b, which has not been included in the manuscripts. The chapter concludes with a discussion of the findings from this phase.

6.2 Description of the Sample

6.2.1 Cancer Patients

Cancer patients were recruited from a consecutive series of patients attending a private radiation oncology centre between July and December 2003. Over this six-month period, 83 patients were identified as eligible potential participants (refer to Section 5.6.1, pages 133-134). Of this pool of eligible participants, 23 patients who met the inclusion and exclusion criteria were deemed by nursing staff to be inappropriate to participate and therefore were not informed of the study. Nursing staff identified reasons such as difficulty coping with the illness and depression, unwell and too frail, requiring continuous oxygen, and short dose radiotherapy pre-surgery, for deeming patients inappropriate. A total of 60 patients were therefore informed of the study, of whom 19 patients consented to participate in the study (23% of total eligible pool; 32% of total informed pool).

Characteristics of participants and non-participants (from total eligible pool) are shown in Table 6.1. There was no significant difference between the two groups based on the available data (age, gender and tumour site), indicating that the sample of participating cancer patients appears to be representative of patients attending the radiation oncology centre over the six-month time period.

Further descriptive details of the sample of cancer patients are shown in Table 6.2. Nineteen patients consented to participate in the study, however prior to commencing data collection, one patient became ill and was admitted to hospital.
No further data were available on this patient except for that shown in Table 6.1. As such, results presented in the manuscript refer to a sample of 18 cancer patients.

**Table 6.1:** Characteristics of participants compared to non-participants from total pool of eligible participants.

<table>
<thead>
<tr>
<th></th>
<th>Participants</th>
<th>Non-Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>19</td>
<td>64</td>
</tr>
<tr>
<td>Age (y) (mean ± sd)</td>
<td>64 ± 14</td>
<td>65 ± 13</td>
</tr>
<tr>
<td>Gender (Male:Female)</td>
<td>11:7</td>
<td>43:21</td>
</tr>
<tr>
<td>Tumour Site (n, %)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>9 (47%)</td>
<td>28 (44%)</td>
</tr>
<tr>
<td>GIT</td>
<td>7 (37%)</td>
<td>21 (33%)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (16%)</td>
<td>15 (23%)</td>
</tr>
</tbody>
</table>

GIT = gastrointestinal tract

**Table 6.2:** Selected characteristics of participating cancer patients (n=18)

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight loss in previous 6 months (%)</td>
<td>2.2 ± 4.6*</td>
</tr>
<tr>
<td>SGA</td>
<td></td>
</tr>
<tr>
<td>A – well nourished</td>
<td>4 (22%)</td>
</tr>
<tr>
<td>B – moderately malnourished or at risk of malnutrition</td>
<td>12 (67%)</td>
</tr>
<tr>
<td>C – severely malnourished</td>
<td>2 (11%)</td>
</tr>
<tr>
<td>Presence of metastases†</td>
<td>3 (17%)</td>
</tr>
<tr>
<td>Tumour recurrence</td>
<td>2 (11%)</td>
</tr>
<tr>
<td>Surgical removal of tumour</td>
<td>5 (28%)</td>
</tr>
<tr>
<td>Radiotherapy treatment</td>
<td>17 (94%)</td>
</tr>
<tr>
<td>Chemotherapy treatment</td>
<td>9 (50%)</td>
</tr>
</tbody>
</table>

SGA = subjective global assessment. * mean ± standard deviation; † pulmonary.

The group varied in the amount of weight lost in the previous six months. Weight change ranged from 6.9% weight gain to 12.3% weight loss over the six months prior to the study, with a mean weight loss of 2% for the group. This amount of weight loss was comparable to that observed in a group of 60 cancer patients (head, neck and gastrointestinal area) also recruited from private radiation oncology centres, who experienced a median (range) weight loss in the previous six months.
of 2.8 (0 – 21)% (Isenring, 2003). The weight loss experienced by cancer patients in this study however is considerably lower than that reported by other studies in groups of single site tumours at diagnosis (Bauer, et al, 2004, Staal-van den Brekel, et al, 1997).

As patients had already commenced treatment (radiotherapy and/or chemotherapy) in this study, some patients reported weight gain following the commencement of treatment. As such, weight loss was also categorised into weight change groups – four patients (22%) had gained weight, three (17%) were weight stable, seven (39%) had lost less than 5% body weight and four (22%) had lost greater than or equal to 5% body weight.

The nutritional assessment of these patients indicated that only a small number of patients were severely malnourished. Without further data on the patients who declined to participate it can only be hypothesised that patients who were more severely malnourished and therefore possibly sicker, may have been more likely to decline participation in the study.

Most patients were attending the radiation oncology centre for treatment of a new primary tumour however small numbers presented with recurrence or metastases. Five patients had undergone surgical removal of the tumour prior to commencing radiotherapy treatment. None of these patients had surgery within the month prior to the study. Medical records noted that complete resection of the tumour had occurred in three patients, while in two the resection was thought to be incomplete. All patients except one had commenced radiotherapy treatment and half were undergoing concurrent chemotherapy treatment at the time of the study.

6.2.2 Healthy Subjects
The age of healthy subjects (n=17) at the time of the study ranged from 39 to 76 years. The mean ± sd body mass index (BMI) of these subjects was 26.3 ± 4.1 kg/m², which is comparable to the national BMI (mean (5th – 95th percentile)) of Australian adults of 26.4 (20.8 – 34.2) kg/m² (Australian Bureau of Statistics, 1995). No other data were available to determine generalisability of the sample of healthy subjects.
6.3 Manuscript 4 – Resting Energy Expenditure in Patients with Solid Tumours Undergoing Anti-Cancer Therapy

Citation:

Date Submitted: –

Date Accepted: –

Contribution of Authors:
MMR was the main author of the manuscript, initiated and designed the study, carried out data collection, statistical analyses, interpretation and discussion of results. DB assisted in the design of the study, interpretation and discussion of results and contributed to the writing of the manuscript. SC initiated the study and assisted in the design of the study. JB assisted with the study design and data collection. PSWD assisted in the design of the study, statistical analyses, interpretation of results and contributed to the writing of the manuscript.

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Manuscript 4 is not available online. Please consult the hardcopy thesis available from the QUT library
Manuscript 4 is not available online. Please consult the hardcopy thesis available from the QUT library.
6.4 Manuscript 5 – Accuracy of the MedGem™ Indirect Calorimeter for Measuring Resting Energy Expenditure in Cancer Patients

Citation:

Date Submitted: June 2004

Date Accepted: –

Contribution of Authors:
MMR was the main author of the manuscript, initiated and designed the study, carried out data collection, statistical analyses, interpretation and discussion of results. SC initiated the study and assisted in the design of the study. JB contributed to the study design and assisted with data collection. PSWD and DB contributed to the study design, data analysis, interpretation and discussion of results and manuscript preparation.

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The text of Manuscript 5 is not available online. Please consult the hardcopy thesis available from the QUT library.
6.5 Additional Results

The following results were not included in either of the manuscripts but address objective 3b relating to the individual predictive accuracy of the seven prediction methods (refer to Table 5.1) in the sample of healthy subjects.

Mean (± sd) measured REE in healthy subjects (n=17) was 5979 ± 1249 kJ. Predicted REE, mean bias and limits of agreement are shown in Table 6.3. Predicted REE from all prediction methods tended to overestimate measured REE however was within clinically acceptable limits of ± 10% for the group of healthy subjects.

Table 6.3: Predicted resting energy expenditure, mean bias and limits of agreement for difference between predicted and measured resting energy expenditure* in healthy subjects (n=17)

<table>
<thead>
<tr>
<th>Method</th>
<th>Predicted REE (kJ/d)</th>
<th>Bias (kJ) †</th>
<th>Limits of agreement (Bias ± 2sd, %)</th>
<th>Proportion within ± 10%‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harris-Benedict</td>
<td>6191 ± 948</td>
<td>212 ± 924</td>
<td>-27 – 34%</td>
<td>52.9%</td>
</tr>
<tr>
<td>Schofield</td>
<td>6320 ± 997</td>
<td>341 ± 907</td>
<td>-25 – 36%</td>
<td>47.1%</td>
</tr>
<tr>
<td>Owen</td>
<td>6384 ± 1028</td>
<td>405 ± 1072</td>
<td>-29 – 43%</td>
<td>23.5%</td>
</tr>
<tr>
<td>Mifflin</td>
<td>6037 ± 1071</td>
<td>57 ± 962</td>
<td>-31 – 33%</td>
<td>52.9%</td>
</tr>
<tr>
<td>Cunningham</td>
<td>6261 ± 1020</td>
<td>282 ± 996</td>
<td>-29 – 38%</td>
<td>29.4%</td>
</tr>
<tr>
<td>Wang</td>
<td>6394 ± 1015</td>
<td>415 ± 995</td>
<td>-26 – 40%</td>
<td>35.3%</td>
</tr>
<tr>
<td>20kcal/kg</td>
<td>6273 ± 1084</td>
<td>294 ± 1076</td>
<td>-31 – 41%</td>
<td>41.2%</td>
</tr>
</tbody>
</table>

* Measured REE = 5979 ± 1249 kJ/d; † Bias = Predicted – Measured; ‡ clinically acceptable limit (± 10% of measured).
Data are mean ± standard deviation

The Mifflin et al (1990) equations produced the smallest mean bias (1%) for this sample, followed by the Harris-Benedict equations (3.5%). The limits of agreement however were wide for all prediction methods, indicating poor prediction for individual healthy subjects. The Harris-Benedict and Schofield equations had the smallest range for the limits of agreement. Although not statistically significant, the Harris-Benedict and Schofield equations tended to underestimate measured REE with increasing REE values, r = -0.36, p = 0.16 and r = -0.30, p = 0.24, respectively.
These results confirm findings of other studies, which have shown wide limits of agreement from the prediction of REE with a number of equations in healthy subjects (Siervo, et al, 2003, Taaffe, et al, 1995).

A common criticism of the Harris-Benedict and Schofield equations has been the lack of representativeness of the populations from which these equations were derived (younger and leaner) to current Western populations. Hence, the development of more recent prediction equations in older populations including overweight and obese subjects and based on more accurate estimates of metabolically active tissue (FFM). Comparison of these newly developed prediction equations with measured REE in this sample of healthy subjects has indicated that the more recently developed methods, with the exception of the Mifflin et al equations, performed considerably worse than the Harris-Benedict and Schofield equations, predicting REE within clinically acceptable limits in only a quarter to less than half of the sample.

6.6 Summary

This study is one of the first studies investigating energy expenditure in cancer patients undergoing anti-cancer therapy. It is also the first study known to the investigator to use the MedGem indirect calorimeter for measuring REE in patients with disease. The aims of this study were to investigate differences in the energy expenditure of cancer patients compared to healthy subjects and to compare different methods for determining energy requirements in people with cancer. To address the aims of this phase a case-control study and two clinical validation studies were conducted.

The results of the case-control study indicated no significant difference in REE between cancer patients and healthy subjects when adjusted for FFM, based on a predetermined clinically meaningful difference of 30%. Only a 10% difference in adjusted-REE was observed, which is similar to that found by other studies (Jatoi, et al, 2001, Staal-van den Brekel, et al, 1997). A clinically significant difference was found between REE measured by the hand-held MedGem indirect calorimeter and traditional indirect calorimetry (VMax 229) both for individual cancer patients and healthy subjects. The results observed in healthy subjects were in contrast to those found by the only published study investigating the accuracy of the MedGem
Possible explanations for these conflicting results may be related to the differences in the traditional indirect calorimeter that was used for comparison with the MedGem and also different definitions for steady state and differences in the operation of the MedGem between the two studies.

These results also confirmed findings of other studies in that currently available prediction methods do not accurately estimate the REE of individual cancer patients (Bauer, et al, 2004) and healthy subjects (Siervo, et al, 2003, Taaffe, et al, 1995). Automatic application of an injury factor of 1.3 or greater with the Harris-Benedict equations for patients with cancer is not appropriate.
CHAPTER 7: DISCUSSION, CONCLUSIONS & RECOMMENDATIONS

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7.1 Introduction

This Doctor of Philosophy research project aimed to address two research questions: 1) How are patients’ energy requirements estimated in clinical practice and what error or variation is introduced by these methods? and 2) Is energy expenditure altered in patients with cancer relative to healthy subjects and what is the most appropriate method for determining the energy requirements of these patients?

The first research question was addressed in Phase 1, a descriptive study that identified a number of areas in relation to current dietetic practice for estimating patients’ energy requirements where there were inconsistencies or errors in practice. Results of this study informed Phase 2, which aimed to address the second research question using hypothesis testing.

This chapter provides an overall discussion of how the findings of the two phases and the five manuscripts collectively address the aims and objectives of the research project (Section 1.2, pages 3-4). The significance of the research is discussed in light of its contribution to the current body of knowledge. This chapter also provides a discussion of the limitations of the study, conclusions of the research project and recommendations for dietetic practice and future research.

7.2 Discussion in Relation to Aims and Objectives

7.2.1 Phase 1: Dietetic Practice

**Aim:** To describe current methods used by dietitians for estimating adult patients’ energy requirements.

1. To describe population groups for which Australian dietitians estimate energy requirements.

Irrespective of the type of patient group, the results of the survey indicated that estimating energy requirements is common practice for most dietitians working in acute care adult hospitals. The survey indicated that enteral feeding appears to primarily determine whether energy requirements are estimated for patients. More than half of the respondents estimate energy requirements for patients requiring...
weight gain, parenteral feeding or critically ill patients. Few dietitians estimate energy requirements for patients requiring weight loss or weight maintenance. Based on these results, it appears that feeding state and not disease state predominantly influences patient groups for whom energy requirements are estimated.

2. To identify the different prediction methods that Australian dietitians use in their daily practice.

This survey has indicated that dietitians use a number of different prediction methods for estimating patients’ energy requirements, including both formal and informal methods. Choice of prediction method appears to be influenced by patient type or situation. Formal calculations (e.g., Schofield and Harris-Benedict equations) are generally used for patients requiring enteral or parenteral nutrition support, malnourished patients and critically ill patients. Based on responses to the case study and usual dietetic practice, the Schofield equations appear to be preferred over the Harris-Benedict equations, as they do not rely on a known height, irrespective of accuracy of the equations. Informal methods include those based on theory (negative energy balance of 500kcal/2000kJ will result in 0.5kg weight loss per week) and experience (eyeball and “guestimate” or standard value). Informal methods are more commonly used for patients requiring weight gain or weight loss.

3. To describe dietitians’ application of prediction equations and injury factors based on a given case study.

This survey identified that, for the case study provided, there was no consensus or consistent approach used among respondents for estimating the energy requirement. The selection of injury factors in the calculation of energy requirement showed inconsistencies both in the reason for selection and the value of the injury factor. Injury factors were also incorrectly applied to prediction equations for which they were not developed. Application of prediction methods for different weight-based nutritional care goals did not translate into differences in calculated energy requirement. Education and training were identified as the main influencing factors in the estimation of energy requirements.

4. To describe the variability of the outcomes of the calculations.

The range of calculated energy requirements was extremely large, approximately 10500kJ/d. This survey had the limitation in that the case study presented was based on a hypothetical case and as such, a measured value for energy
expenditure was not known. It was expected however that the estimates of energy requirement would have fallen within a narrower range. Without a measurement of energy expenditure, the mean calculated energy requirement was assumed to be close to the truth, for the purpose of estimating the variation. Based on a predetermined range of $\pm 3-6\%$ of energy expenditure for weight maintenance, only one third of respondents calculated energy requirement within this degree of precision. The large variation in calculated energy requirements observed tends to indicate that there is error inherent with the use of prediction methods. This error may result in negative outcomes associated with underfeeding or overfeeding.

7.2.2 Phase 2: REE in Cancer

**Aim:** To quantitatively investigate differences in energy expenditure of cancer patients compared to healthy controls.

1. To compare the measured resting energy expenditure of people with solid tumours to people without cancer.

   \[ H_01: \text{There is no difference in the measured REE of people with solid tumours compared to people without cancer.} \]

There was no significant difference in measured REE in cancer patients compared to healthy subjects, based on the predetermined clinically meaningful difference of 30%. In this sample of cancer patients, which included patients with cancers of the lung and gastrointestinal tract undergoing anti-cancer therapy, who had experienced minimal weight loss and most of whom were moderately malnourished or at risk of malnutrition, only a non-significant 10% higher measured REE was observed compared to healthy subjects.

These results support more recent literature (Fredrix, et al, 1991, Jatoi, et al, 2001, Staal-van den Brekel, et al, 1997), which is in contrast to the often common perception that energy expenditure is increased in cancer patients due to metabolic alterations caused by the tumour. In Figure 2.2 (page 12) it can be seen that the influence of disease and injury on BMR has been suggested to occur through direct effects on metabolic rate and/or indirectly through alterations in body composition (FFM). With the statistical approach that was used, REE was adjusted for differences in FFM between the two groups, resulting in a remaining 10% difference between cancer patients and healthy subjects. This form of analysis, although the most appropriate for analysing energy expenditure data between groups, assumes
that the composition of FFM (ie proportion of FFM as high metabolic activity organs and low metabolic activity tissues) between cancer patients and healthy subjects is similar. There is sufficient evidence however to suggest otherwise, particularly in patients who have lost significant amounts of body weight (Heymsfield, 2002). Without sophisticated methods for measuring the composition of FFM we cannot discount the influence of cancer on altering BMR through body compositional changes.

The small amount of weight loss experienced by cancer patients in this study, may have accounted for the lack of association between weight loss and FFM-adjusted REE, whereas studies that have found significant relationships have included cancer patients who have lost greater than 10% of body weight (Hansell, et al, 1986, Staal-van den Brekel, et al, 1997). Therefore we cannot conclude on the basis of this study, that the weight-losing state does not affect REE.

The unexpectedly higher FFM-adjusted REE observed in patients who had undergone tumour resection is of interest. A common perception appears to be that the effect of cancer on REE is diminished once the tumour is removed. This has also been supported by literature showing reductions in REE in cancer patients post-operatively (Arbeit, et al, 1984, Luketich, et al, 1990). In the current study however, only a small number of patients had undergone surgery and as such it is not possible to determine characteristics of this group. These results therefore are only speculative.

**Aim:** To compare different methods for determining energy requirements in people with cancer.

2. To investigate, in people with solid tumours and people without cancer, the accuracy of a new portable device for measuring energy expenditure compared to a traditional validated method.

   H02a: There is no difference in the energy expenditure measured by the new device and the traditional method in people with solid tumours.

   H02b: There is no difference in the energy expenditure measured by the new device and the traditional method in people without cancer.

This study found a clinically significant difference (greater than ± 5%) between REE measured by the MedGem and REE measured by the VMax 229 for individual cancer patients and healthy subjects. The MedGem only measured REE within
clinically acceptable limits ($\pm 5\%$) of the VMax 229 for healthy subjects at the group level only. To be of use in a clinical setting however, the MedGem needs to measure REE within clinically acceptable limits for individuals. The results of this study showed a large variation in measured REE from the MedGem in both cancer patients and healthy subjects, with individuals REE measured as much as 45% below, up to 20 – 30% above REE measured by the VMax 229.

The only published study that has compared REE measured by the BodyGem™ with traditional indirect calorimetry found very positive results indicating that the BodyGem accurately and reliably measured VO$_2$ and calculated REE in healthy subjects (Nieman, et al, 2003). This study was supported by a grant from HealtheTech Inc, the manufacturers of the MedGem and BodyGem devices. This study also changed the normal operations of the BodyGem device so that the device used the same steady state criteria as the traditional indirect calorimeter (Douglas Bag). To be deemed an accurate measurement instrument, validation studies for the device should be conducted using the device as it is intended in practice.

The current study measured REE with the MedGem as it is to be used in practice, and found significant differences when compared to a traditional indirect calorimeter (VMax 229). Differences between the two indirect calorimeters may be due to bias introduced by the different oxygen analysers and steady state criteria, the assumption of an RQ of 0.85 with the MedGem or the larger diameter mouthpiece used with the VMax 229. Without a better understanding of these potential sources of error, the findings of this study suggest that the MedGem portable indirect calorimeter may not be appropriate for measuring REE for individual cancer patients or healthy subjects.

3. To compare the individual agreement of actual measurements of energy expenditure with estimates from prediction equations in people with solid tumours and people without cancer.

$H_{03a}$: There is no difference between measured REE and predicted REE in people with solid tumours.

$H_{03b}$: There is no difference between measured REE and predicted REE in people without cancer.

This study found that all prediction methods estimated REE outside clinically acceptable limits of $\pm 10\%$ for individual cancer patients and healthy subjects compared to measured REE. All prediction methods, with the exception of the
Harris-Benedict equations in combination with an injury factor of 1.3 for cancer patients, estimate REE within clinically acceptable limits only at the group level for both cancer patients and healthy subjects. However, it is individual predictive accuracy that is of importance in the clinical setting.

In calculating REE from the prediction equations, an adjusted weight instead of actual weight was used with the Harris-Benedict equations for subjects with a BMI greater than 29kg/m². There is no evidence or recommendations to suggest using a weight other than actual weight for the remainder of the prediction equations. In this sample, seven (39%) cancer patients and four (23%) healthy subjects had a BMI greater than 29kg/m². As four of the remaining six prediction equations used weight in the calculation, the larger proportion of body weight comprised of low metabolic activity adipose tissue and skeletal muscle in these people may influence the estimates of REE.

No prediction equations have been developed specifically for patients with cancer. This study has confirmed previous literature that current prediction methods derived from healthy populations are not appropriate for predicting the REE of individual cancer patients (Bauer, et al, 2004) or healthy subjects (Siervo, et al, 2003, Taaffe, et al, 1995).

4. To compare the individual agreement between measurements of REE using different steady state criteria.
   
   \[ H_0^{4a} \text{: There is no difference in REE measured using five-minute steady state criteria and REE measured using four-minute steady state criteria.} \]

   \[ H_0^{4b} \text{: There is no difference in REE measured using five-minute steady state criteria and REE measured using three-minute steady state criteria.} \]

This study found no clinically significant difference (± 2%) for individual subjects between REE measured by 4-min SS compared to 5-min SS, but use of 3-min SS criteria produced measurements of REE that fell just outside the clinically acceptable limits (-2 to 3%). In certain clinical contexts however, the error allowed for by using 3-min SS may be acceptable. For example, if measurement of REE is possible, however 5-min SS is not achieved, use of 4-min SS or even 3-min SS will produce an estimate of REE in a larger proportion of subjects that is well within the limits of the alternative, prediction equations.
7.3 Towards Better Practice

This research project has been developed and discussed in relation to clinical practice. In the current environment of evidence-based medicine, it is essential that practice evolve with the growing body of literature and evidence. The findings of this research project have highlighted a number of areas for improvement in the practice and teaching of dietetics.

A preliminary framework of factors that influence dietitians’ practice for estimating patients’ energy requirements was used to inform the development of the Phase 1 survey (Table 3.1, page 62). Results from the survey indicate that the ‘Education’ and ‘Importance’ constructs of this framework appear to have the greatest influence on dietitians’ practice. The influence of education was identified both subjectively and objectively. Respondents self-reported that education was the prime influencing factor in their estimation of energy requirements and bivariate analyses indicated that year of completing dietetic education was associated with the prediction method used in the calculation. There was no evidence to suggest that education institution influenced practice.

As current methods used by Australian dietitians for estimating energy requirements appear to be varied and inconsistent, resulting in large variations in estimates of energy requirements, these findings suggest that strategies to improve practice should target standardisation of education practices.

Further results from the survey indicate that greater importance appears to be placed on the method of feeding for estimating patients’ energy requirements, rather than disease status or weight status. Dietitians reported that almost all estimate energy requirements for patients requiring enteral feeding, more formal prediction methods are used for patients on enteral or parenteral feeds and higher importance is rated for accurately estimating energy requirements for tube fed patients compared to patients on food-based diets.

This suggests that current dietetic practice for estimating patients’ energy requirements is determined by the patients’ feeding state rather than the disease state. Use of enteral tube feeding or parenteral nutrition provides a level of control over a patient’s total daily energy intake. A number of studies have compared delivered energy intake from enteral nutrition with prescribed energy requirement.
More than one third (36%) of mechanically ventilated patients in long-term acute care hospitals (McClave, et al, 1998) and over a quarter (27%) of critically ill patients (De Jonghe, et al, 2001) receiving enteral nutrition, received less than 90% of their prescribed energy requirement. Discrepancies between delivered enteral nutrition and prescribed energy requirement are often a result of cessation of enteral feeding due to diagnostic procedures, tube displacement, routine nursing care or gastrointestinal dysfunction (De Jonghe, et al, 2001, McClave, et al, 1999). In two thirds of the cases however, cessation of enteral nutrition was deemed avoidable (McClave, et al, 1999). Discrepancy between prescribed energy requirement and delivered energy intake via parenteral nutrition on the other hand is minor (De Jonghe, et al, 2001).

Food-based intake, particularly in acutely and chronically ill patients with poor appetites, on the other hand is difficult to control to ensure intake is equivalent to prescribed requirement. In a clinical setting, dietitians rely on food records as measures of energy intake, the accuracy of which is questionable (Nelson, 1997). There is no literature regarding discrepancies between energy intake and energy requirement in ill patients on food-based diets.

A greater focus on accurately estimating energy requirements for patients receiving enteral nutrition does not therefore appear warranted. Prescribed energy requirements are related to nutrition care goals, which are in turn related to the specific disease state and individualised to the patient. Focus on the accuracy of estimating patients’ energy requirements should therefore be related to the disease state and not the feeding state, and subsequently on the actual energy intake.

Phase 2 of this research project has indicated that increases in energy expenditure in cancer patients may not be as prominent as often thought. Weight loss observed in patients with cancer is therefore a likely result of decreased energy intake in combination with alterations in energy expenditure (Bosaeus, et al, 2001, Burke, et al, 1980, Lindmark, et al, 1984, Toth, 1999, Toth & Poehlman, 2000). Any increases in REE in patients with cancer or other chronic and acute illnesses are often associated with a concomitant decrease in physical activity that is usually greater than the increase in REE, resulting in an overall reduction in total daily energy expenditure (Toth, 1999). This again highlights the importance of monitoring energy intake in relation to energy requirement.
A large variation in FFM-adjusted REE in the sample of cancer patients was observed, indicating a highly variable individual response in REE to cancer. Practical tools for measuring REE in a clinical setting would therefore be valuable to dietitians and other health care professionals. Results of this study suggest that the MedGem indirect calorimeter does not appear to be appropriate for measuring REE in patients with cancer, including lung and gastrointestinal cancer, with minimal weight loss. The device however may still be appropriate for measuring REE in other disease or injury populations, not studied here.

Prediction equations estimated individuals’ REE within similar limits to that measured by the MedGem, without the cost. None of these equations however were appropriate for estimating REE of individual cancer patients or healthy subjects. Measurements of energy expenditure using traditional indirect calorimetry, the most accurate method for determining energy requirements, are rarely available or practical in a clinical setting. Due to the poor individual predictive accuracy of any of the current prediction equations, monitoring of actual energy intake and patient outcomes is vital. Patient outcomes to be monitored may include weight, lean body mass, nutritional status or other parameters specific to the individual patient’s condition. An understanding of the degree to which energy intake can differ from energy requirement while still achieving nutritional care goals and avoiding complications associated with under- or overfeeding is warranted, however it is likely to be patient-specific.

7.4 Limitations of the Research

The limitations of the research project are identified below. Steps taken to minimise limitations and discussion of results in light of these limitations have also been included. These relate to sampling, selection and confounding bias, inadequate sample size and the measurement tools used.

In case-control studies the cases and controls should be drawn from the same population so that ideally, the only difference between the two groups is the exposure (or presence of disease). In this study, the sampling frame differed between cancer patients and healthy subjects. Factors that influence energy expenditure however have previously been discussed. The main determinant of REE is body composition (FFM). Demographic and environmental factors, which
may be associated with the sampling frame used, do not directly influence REE but may impact on body composition. Instead the two groups were group matched by gender on age, weight and height to reflect a similar FFM across cancer patients and healthy subjects.

For case-control studies it is also ideal that the person undertaking data collection is blind to the case or control status of participants. In this study, the investigator recruited all participants and undertook all data collection and therefore it was not possible to be blind to the status of participants. As the outcome variable was objectively measured by the indirect calorimeter this is unlikely to have biased results.

The number of patients who consented to participate in the study was small in comparison to the total eligible pool (23%). As such there is the potential for selection bias to be introduced. A comparison of known characteristics between participants and non-participants indicated no significant difference between the groups for gender, age or tumour site. These variables were the only data provided to the investigator on the total eligible pool and therefore it is not known whether the groups differed with respect to FFM, tumour stage, weight loss in the previous six months and/or nutritional status. The results of this study can therefore only be generalised to cancer patients similar to our sample. These are patients with lung and gastrointestinal cancer, who have experienced mild to moderate weight loss, are moderately malnourished or at risk of malnutrition and undergoing anti-cancer therapies.

The recruitment of cancer patients was restricted by time constraints. The low consent rate of cancer patients over the six-month recruitment period meant that the clinical validation study comparing the MedGem and VMax 229 was underpowered. Due to this, interpretations of significance of results for all hypotheses were primarily based on assessing differences for clinical meaningfulness first and foremost, followed by statistical significance.

A well-established confounder of REE is FFM, which was adjusted for in the case-control study. Weight loss was identified as another potential confounder but found not to be associated with FFM-adjusted REE. Also, as the sample of cancer patients was heterogeneous in terms of tumour site, stage and current treatment, effect modification by these variables was likely. Analytical measures to account for these
effect modification variables were attempted, however the relatively small sample sizes that resulted from the stratification limited the extent to which these effects could be explored. In addition, as the health of control subjects was self-reported and exclusions were based on limited health conditions, it is not possible to completely discount the potential effect of other conditions on the REE of control subjects.

Use of validated objective tools assists in reducing error in the measurement of dependent and independent variables. The ventilated hood is the most recognised portable indirect calorimetry collection system. This study used an indirect calorimeter with a mouthpiece and noseclip for collection of expired air (VMax 229). The choice of indirect calorimeter was primarily to minimise participant burden. The VMax 229 was the only indirect calorimeter available within the vicinity of the radiation oncology centre (WCCC) where cancer patients were recruited. Patients’ data collection was coordinated with their treatment at the WCCC, so that they were only required to travel to the one place on the day of data collection.

The influence of the mouthpiece on REE would be likely to be similar between the group of cancer patients and healthy subjects. As the case-control study primarily assessed the difference in REE between the two groups it could be assumed that the absolute difference between cancer patients and healthy subjects would be the same whether a mouthpiece or ventilated hood was used to collect expired air.

As the MedGem was also used with a mouthpiece, both indirect calorimeters used the same collection system, however the mouthpiece with the VMax 229 was larger. Weissman et al (1984) found that the effect of mouthpieces on REE compared to ventilated hoods was dependent on the size of the mouthpiece. Therefore differences in the mouthpieces may have introduced systematic overestimation in the measurement of REE with the VMax 229.

This study did not investigate the reproducibility of the VMax 229 or the MedGem indirect calorimeter due to resource limitations and the need to minimise participant burden, particularly in the group of cancer patients. Reproducibility of the MedGem had previously been assessed to be high (Nieman, et al, 2003) and therefore was not repeated in this study. Reproducibility of traditional indirect calorimetry methods is often reported to be high, with measurement error in the order of less than 5% (refer to Section 4.3.9, page 110). Although reproducibility of the VMax 229 was not...
measured in this study, if it is assumed to be of a similar magnitude to that reported by other studies, it is highly unlikely that any of the conclusions from these studies, where limits of agreement were approximately ± 30 – 40%, would be altered. That is, even with minimal measurement error in the VMax 229, neither the MedGem nor the prediction methods would be considered clinically acceptable for individual patients.

Measurements of REE are normally conducted in the supine position. In this study all subjects had REE measured in the semi-reclined position, as pooling of saliva and difficulties swallowing are often experienced when using mouthpieces in the supine position. As the position of REE measurement was constant between cancer patients and healthy subjects and between the VMax 229 and MedGem, it is unlikely to have influenced the results.

Two technicians conducted the measurements of REE with the VMax 229. To minimise the bias that may be introduced by using two technicians, the investigator was present during all measurements. Once measurements were terminated, the investigator was responsible for selecting the steady state readings from the indirect calorimeter software, so this was consistent across all participants.

These limitations have minor implications for the discussion of the results. The difference in REE observed between cancer patients and healthy subjects in this study cannot be generalised to patients with cancer who have experienced significant weight loss (≥ 10% initial body weight). Although comparison of the MedGem with the VMax 229 in both cancer patients and healthy subjects was underpowered due to the limited sample size, interpretation of results for clinical meaningfulness indicated that there was a significant difference between the measurement methods. The traditional indirect calorimeter (VMax 229) selected for use in this study may have introduced a systematic overestimation of REE in the comparison with the MedGem indirect calorimeter. The bias observed between the two indirect calorimeters was therefore in the expected direction however there is little evidence to quantify the degree of overestimation introduced by the VMax 229. These limitations can be addressed with further research.
7.5 Conclusions

In a clinical setting patients’ energy requirements are often estimated using prediction equations, as measurements of energy expenditure are rarely available, too expensive, time-consuming and are impractical. A number of prediction equations have been developed, primarily in healthy populations. Population-specific equations are recommended in practice however no equations have been developed specifically for cancer patients. Only one study has previously looked at the individual predictive accuracy of a range of prediction equations in patients with pancreatic cancer. There is sufficient evidence to suggest that effective nutrition management of the patient with cancer will improve patient outcomes such as weight, nutritional status, quality of life and survival. The first step towards effective nutritional care is to determine patients’ requirements including energy and secondly, ensuring intake is equal to requirements. As such the first challenge is to accurately determine the patient’s energy requirement.

The results of this research project have indicated that dietitians’ practice for estimating adult patients’ energy requirements is highly variable. These inconsistencies in practice appear to be due to a lack of knowledge regarding the derivation, application and limitations of prediction methods. Choice of prediction method appears to be influenced by the limited patient information often available in a clinical setting (eg weight and/or height) and what dietitians learned in their initial dietetic education and training. The importance of accurately estimating energy requirements and the types of patients for whom dietitians estimate energy requirements appears to be heavily influenced by feeding method. That is, patients who require enteral feeding are more likely to have their energy requirement calculated by more formal methods and will have greater emphasis placed on ensuring energy requirements are calculated accurately.

Findings from these studies have shown that REE in cancer patients may not be as elevated as originally thought. Only a 10% higher FFM-adjusted REE was observed in patients with solid tumours, including tumours of the lung and gastrointestinal tract, with minimal weight loss and who are moderately malnourished, compared to healthy control subjects of similar age, weight and height. In this sample of cancer patients and healthy subjects the portable MedGem indirect calorimeter did not measure individual REE within clinically acceptable limits compared to a traditional indirect calorimeter (VMax 229).
These studies provide evidence that prediction equations, including historical (e.g., Harris-Benedict) and more recently developed equations, are only appropriate to estimate REE at the group level. No method was acceptable for estimating REE of individual cancer patients or healthy subjects, which is clinically the more relevant estimate. Typical use of an injury factor of 1.3 in combination with the Harris-Benedict equations, consistently overestimated measured REE in cancer patients.

This research project provides evidence to suggest that reducing the time period of steady state, during which time VO\textsubscript{2}, VCO\textsubscript{2}, RQ and \(V_E\) change by \(\leq 10\%\), to four-minutes, or in some contexts even three-minutes, compared to the standard five-minutes, does not affect the accuracy of REE measurements, while also increasing the proportion of subjects with a valid REE measurement. Achievement of steady state, in combination with careful calibration of equipment, adherence to standard conditions for testing and assessment of data for physiological validity, will improve the accuracy of short-term measurements of REE.

Collectively, the results of this PhD research project have indicated that current practical methods for determining patients’ energy requirements in a clinical setting do not accurately predict the resting energy expenditure of individual subjects, healthy or with cancer. Greater emphasis should therefore be placed on the second step within the nutritional care process – ensuring intake meets requirements. For this to occur, dietetic practice should be focused on monitoring both patients’ actual energy intake and patient outcomes, including weight and other patient-specific parameters, to determine whether energy requirements are being met.

### 7.6 Recommendations for Dietetic Practice

Findings of these studies and review of the literature have identified aspects of dietetic practice and teaching that require change. A number of recommendations to improve practice are provided.

The first step to improving practice is to target dietetic education so that newly trained dietitians are taught appropriate practices. Dietetic education needs to be modified to reflect current evidence regarding the relative quality of methods for estimating patients’ energy requirements. As part of their education (both initial
dietetic education and continuing professional development) dietitians require an understanding of the derivation, application and particularly the limitations of prediction methods.

None of the currently available prediction equations are accurate for estimating REE and hence energy requirements of individual cancer patients and healthy subjects. However when measurement of energy expenditure is not available, there are currently no other practical methods available to dietitians for accurately assessing patients’ energy requirements. A number of practical recommendations are therefore suggested to assist dietitians in estimating patients’ energy requirements.

Firstly, prediction methods should be used to provide an estimate or “ball park” of energy requirements only. The Harris-Benedict, Schofield, Owen et al and Mifflin et al equations and the kcal/kg method, estimate REE within relatively similar (but wide) limits of agreement for cancer patients and healthy subjects. The Cunningham and Wang et al equations also predict REE within similar limits, although slightly wider. These two methods however rely on a measure of FFM, which may not be readily available in clinical practice. Choice from these prediction methods may therefore be influenced by the amount of data available on the individual patient (eg weight and/or height), or by comfort and familiarity with the equation. Either way, these equations should only be used to provide a starting figure.

For people with a BMI greater than 29 kg/m² there is evidence to recommend using an adjusted weight in the calculation of REE from the Harris-Benedict equations. An adjusted weight should also be used with the Schofield equations as these equations were derived from relatively leaner populations. The kcal/kg method should also use an adjusted or ideal weight for obese people, as use of actual weight would greatly overestimate REE due to the greater proportion of body weight as low metabolic activity tissue. However there is no evidence for how adjusted weights should be calculated for these prediction methods.

Previous studies in the USA have provided evidence for use with the Harris-Benedict equations of an adjusted weight defined as IBW + 50%(actual – IBW), where IBW is calculated from the Hamwi equation. In Australia, IBW is usually estimated based on BMI cut-offs. IBW defined by the Hamwi equation equates to approximately a BMI of 21 kg/m² for females and a BMI of 23.5 kg/m² for males.
These prediction equations estimate REE or BMR. To estimate patients' energy requirements an injury factor(s) and activity factor are often included with the estimate of REE. If energy requirements are estimated this way, the two factors should be added and not multiplied. For example:

\[ \text{Energy requirement} = \text{BMR} \times (1 + \%\text{IF} + \%\text{AF}) \]

Where:  
\[ \%\text{IF} = \text{IF} - 1 \]
\[ \%\text{AF} = \text{AF} - 1 \]

IF: injury factor; AF: activity factor.

Furthermore, overuse of specific injury factors should be limited. Common injury factors were derived in the 1970’s. Since that time advances in medical treatment have reduced the effect of certain injuries (eg burns) on energy expenditure and as such these injury factors are unlikely to apply to current medical conditions.

This study provided evidence that use of an injury factor of 1.3 with the Harris-Benedict equations for patients with cancer should be restricted. An injury factor should only be used in cases where there is clear evidence of metabolic disturbances, for example patients with significant weight loss in the presence of sufficient energy intake.

Any estimates of energy requirements should be individualised to the patient or patient type. As prediction methods may either overestimate or underestimate REE, dietitians should determine for each particular patient whether it is safer to err on the side of underfeeding or overfeeding. For example, in critically ill patients there is sufficient evidence to recommend slight underfeeding. It is easier to underestimate energy requirements using the kcal/kg method and therefore this method is often used with these patients. Particularly if slight underfeeding is justified, an adjusted weight should be used with this method for overweight and obese subjects.

Energy requirements could also be estimated if accurate assessments of energy intake, weight and/or weight change are known. For example, for patients requiring weight gain or weight loss, the patient’s current energy intake can be assessed and if weight has been stable on this energy intake, then a constant energy value (eg 500kcal/2000kJ) can be added or subtracted, respectively, to determine energy requirement.
In the small number of cases where energy expenditure is measured, particularly in spontaneously breathing patients, steady state should be defined as a four-minute or three-minute period during which VO₂, VCO₂, RQ and VE change by ≤ 10%. By avoiding the conventional five-minute steady state criterion, this will increase the proportion of subjects who will achieve steady state without compromising measurement accuracy.

Given the very approximate nature of all practically available methods for estimating energy requirements, patients should be regularly monitored for both energy intake and patient outcomes, to ensure energy requirements are being met. Which patient outcomes to monitor will be specific to the individual patient, but ideally weight should be measured if possible. Body composition such as fat free mass and nutritional status using the Patient-Generated Subjective Global Assessment (PG-SGA) could also be monitored. Determining appropriate patient outcomes to monitor may also require identifying from the literature easily measurable disease-specific parameters that will reflect adequacy of energy intake (i.e. whether energy requirements are met).

To assist the change of practice, results and recommendations from this research project should be disseminated widely to individual practitioners and those educating dietitians in universities. This can occur through publication of results, presentation at national and international conferences and via the professional association networks (for example, newsletter, journal, continuing professional development events).

### 7.7 Recommendations for Future Research

Recommendations for future research to address limitations of, or extend from, the current research include:

- Further studies comparing REE measurements in patients with solid tumours who have experienced severe weight loss and are undergoing anti-cancer therapies to healthy subjects. This will assist in determining alterations in REE in weight-losing cancer patients, as the sample of cancer patients included in the current study had experienced minimal weight loss.
- Further studies comparing REE measurements in patients following tumour resection while undergoing radiotherapy and/or chemotherapy to healthy
subjects. Such a study would provide evidence regarding the REE of this population and determine whether this population truly differs from cancer patients with the tumour insitu. This knowledge would have implications for the nutritional management of these patients.

- Further studies investigating the accuracy of the MedGem indirect calorimeter in clinical settings, ensuring adequate sample size. For example, comparison of REE measurements with the MedGem indirect calorimeter and traditional indirect calorimeter using a ventilated hood, in patients with cancer and in patients with other diseases or injuries. The current study has confirmed that currently available, practical prediction equations are not appropriate for estimating REE for individual patients. Practical tools, such as the MedGem indirect calorimeter if shown to be accurate, would be ideal for measuring energy expenditure of individual patients at the bedside. Further studies to address any limitations of the current study would assist in confirming or disputing the results that were observed.

- Further studies investigating the reproducibility of REE measurements using the MedGem indirect calorimeter. The current study did not investigate the reproducibility of the MedGem as the previous published study had indicated high within and between day reliability of the BodyGem. In retrospect, considering the distinct differences in the results between the current study and the published study, repeated measurements of REE with the MedGem should have been undertaken to confirm the reported results.

- Further studies of current dietetic practice to identify what aspect of the prediction method (ie choice of prediction equation, injury factor, activity factor or weight) is responsible for the large variation in estimated energy requirement. Such a study would require a considerably greater sample size than that achieved in the present research, to allow for the multiple combinations of prediction methods.

- Studies investigating the degree to which patients can be underfed or overfed while still avoiding negative outcomes associated with underfeeding or overfeeding. Results of such a study would provide direct clinical application however it is highly likely that the degree of feeding before complications are observed would be patient-specific and vary from patient to patient.

- Ideally, a meta-analysis of studies that have measured REE in cancer patients to develop cancer-specific regression equations. However, considering the range of regression equations reviewed here, it is unlikely that such equations would produce an acceptable level of individual predictive accuracy.
This research project has found that currently available practical methods for estimating patients' energy requirements are not accurate for individual patients with cancer of the lung or gastrointestinal tract receiving anti-cancer treatment or healthy subjects, and application of these methods varies greatly in practice. Education of dietitians regarding the correct application and limitations of these prediction methods and future research addressing the methodological limitations of this research project are warranted.
APPENDICES
Appendix A:  Survey (Phase 1)
4 September 2001

Dear Dietitian

I am writing to ask your assistance in an important study that is being conducted by the Queensland University of Technology, as part of a Doctorate of Philosophy research project. The study is aimed at investigating the energy requirements of people with chronic diseases. This survey will identify the methods dietitians use in practice for estimating patients’ energy requirements.

The survey has been sent to dietitians working in both public and private acute care hospitals throughout Australia. Our pilot tests have shown that it should take approximately 15 minutes to complete.

The survey is aimed at identifying methods by which dietitians estimate energy requirements within their usual dietetic practice, using one case as an example. The focus is on what you usually do in your daily dietetic practice. The survey results will assist in developing guidelines for estimating energy requirements for people with chronic diseases. The more people that complete the survey, the better our study will be.

Responses are anonymous and confidentiality is assured. The surveys have been coded for hospital type, not for individuals, to assist in following up non-respondent hospitals. We will be looking at the total information from all respondents, and not at individual answers. The survey has received ethical clearance from the Queensland University of Technology Human Research Ethics Committee.

Please answer all questions and return the survey in the stamped self-addressed envelope provided, before September 24. If you would like a summary of the findings please fill in the details on the form provided and return with the survey. Please note that details on this form will be kept separate to survey responses.

If you have any queries regarding this survey please contact Marina Koutsoukos on (07) 3864 5853, or email, m.koutsoukos@qut.edu.au. If you prefer, you may contact my supervisor, Associate Professor Sandra Capra on (07) 3864 5870, or the secretary of the QUT Ethics Committee, Mr Gary Allen, on (07) 3864 2902.

Thank you for your cooperation in completing this questionnaire.

Yours sincerely

Marina Koutsoukos
B Hlth Sc (Nutr & Diet) Hons1
APD

Sandra Capra
PhD APD
4 September 2001

Dear Director of Nutrition & Dietetic Services

I am writing to ask your assistance in an important study that is being conducted by the Queensland University of Technology, as part of a Doctorate of Philosophy research project. The study is aimed at investigating the energy requirements of people with chronic diseases. This survey will identify the methods dietitians use in practice for estimating patients’ energy requirements. The survey results will assist in developing guidelines for estimating energy requirements for people with chronic diseases.

Enclosed is a number of survey kits (cover letter, survey, summary form and stamped envelope) to be distributed to dietitians within the department/hospital.

What do you have to do?
1. If I have sent the same number of surveys as there are dietitians, please provide each dietitian with a survey kit to complete and return before September 28.
2. If I have sent fewer surveys than the number of dietitians in the department, please complete the survey only for the number of dietitians for which surveys have been provided. There is no need to obtain additional copies of the survey. I would encourage that you select dietitians with a range of experience to complete the questionnaire (ie those with few years experience and those with many years experience).
3. If I have sent more surveys than the number of dietitians in the department, please complete the number of surveys for which there are dietitians and return the extra (incomplete) surveys in the envelope(s) provided for our records.

Please encourage dietitians to answer all questions and return the survey in the stamped self-addressed envelope provided, before September 28.

If you have any queries regarding this survey please contact Marina Koutsoukos on (07) 3864 5853, or email, m.koutsoukos@qut.edu.au. If you prefer, you may contact my supervisor, Associate Professor Sandra Capra on (07) 3864 5870, or the secretary of the QUT Ethics Committee, Mr Gary Allen, on (07) 3864 2902.

Thank you for your cooperation in completing this questionnaire.

Yours sincerely

Marina Koutsoukos
B Hlth Sc (Nutr & Diet) Hons1
APD

Sandra Capra
PhD APD

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Appendices
17 September 2001

Dear Dietitian

Two weeks ago a survey about the methods dietitians use for estimating patients’ energy requirements was mailed to you. If you have already completed and returned the survey to us, please accept our sincere thanks.

If you have not completed and returned the survey, could you please do so today. We would be very grateful for your response because this will help assist us in developing guidelines for estimating the energy requirements of people with chronic diseases.

If you did not receive the survey, or have misplaced it, please call Marina Koutsoukos on 07 3864 5853 and we will mail another one to you straight away.

Yours sincerely

Marina Koutsoukos
B Hlth Sc (Nutr & Diet) Hons1
APD

Sandra Capra
PhD APD
17 September 2001

Dear Director of Nutrition & Dietetic Services

Two weeks ago surveys about the methods dietitians use for estimating patients’ energy requirements were mailed to dietitians in your department. If the dietitians have already completed and returned the survey to us, please accept our sincere thanks.

If they have not completed and returned the survey, could you please encourage them to do so today. We would be very grateful for your responses because they will help assist us in developing guidelines for estimating the energy requirements of people with chronic diseases.

If you did not receive the surveys, or have misplaced them, please call Marina Koutsoukos on 07 3864 5853 and we will mail another one to you straight away.

Yours sincerely

Marina Koutsoukos  Sandra Capra
B Hlth Sc (Nutr & Diet) Hons1  PhD APD
APD
16 October 2001

Dear Dietitian

Approximately six weeks ago we mailed a survey to you about methods dietitians use for estimating patients’ energy requirements. To the best of our knowledge, this survey has not yet been returned. Please advise us if you have returned the survey.

The comments from the majority of people who have already returned the survey identify the problems dietitians face in estimating patients energy requirements and the varying methods and approaches that are used. These results are going to be very useful in developing guidelines for estimating energy requirements for people with chronic diseases.

We are writing again because your survey is important to our study. It is only by hearing from everyone that we can be sure our results accurately reflect current dietetic practice. Whether or not you usually estimate energy requirements for patients, we need to hear from you.

Our pilot tests have shown that the survey should take approximately 15 minutes to complete. Responses are anonymous and confidentiality is assured. The surveys have been coded for hospital type, not for individuals, to assist in following up non-respondent hospitals. We will be looking at the total information from all respondents, and not at individual answers.

We hope that you will complete the survey and return it to us as soon as possible. If you would like a summary of the findings please fill in the details on the form provided and return with the survey. Please note that details on this form will be kept separate to survey responses.

If you have any queries regarding this survey please contact Marina Koutsoukos on (07) 3864 5853, or email, m.koutsoukos@qut.edu.au.

Thank you very much for helping us with this important study.

Yours sincerely

Marina Koutsoukos     Sandra Capra
B Hlth Sc (Nutr & Diet) Hons1   PhD APD
APD
16 October 2001

Dear Director of Nutrition & Dietetic Services

Approximately six weeks ago we mailed surveys to your department about methods dietitians use for estimating patients’ energy requirements. To the best of our knowledge, all of these surveys have not yet been returned. Please advise us if the surveys have been returned.

The comments from the majority of people who have already returned the survey identify the problems dietitians face in estimating patients energy requirements and the varying methods and approaches that are used. These results are going to be very useful in developing guidelines for estimating energy requirements for people with chronic diseases.

We are writing again because your surveys are important to our study. It is only by hearing from everyone that we can be sure our results accurately reflect current dietetic practice.

Enclosed is a number of survey kits (cover letter, survey, summary form and stamped envelope) to be distributed to dietitians who have not yet completed and returned the survey.

What do you have to do?
1. If there are dietitians who have not yet completed and returned the survey, please provide them with a new survey to complete and return to us soon.
2. If all of the dietitians have already completed the survey, or if I have sent more surveys than the number of dietitians in the department, please return the extra (incomplete) surveys in the envelope(s) provided for our records. This is very important for us to determine our sample size.

Please encourage dietitians to answer all questions and return the survey in the stamped self-addressed envelope provided as soon as possible. If you have any queries regarding this survey please contact Marina Koutsoukos on (07) 3864 5853, or email, m.koutsoukos@qut.edu.au.

Thank you very much for helping us with this important study.

Yours sincerely

Marina Koutsoukos
B Hlth Sc (Nutr & Diet) Hons1
APD

Sandra Capra
PhD APD

B Hlth Sc (Nutr & Diet) Hons1
Appendix C: REE in Cancer: Literature Review Tables
<table>
<thead>
<tr>
<th>First Author (Year)</th>
<th>Patient Population</th>
<th>Method</th>
<th>Results</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warnold (1978) Sweden</td>
<td>10 Ca 9 Co</td>
<td>Mix – GI, sarcoma Hospital for ≥ 4 weeks –</td>
<td>↑ REE (kcal/d) in Ca compared to Co When influence of weight, height and BCM were eliminated, REE was higher in Ca compared to Co.</td>
<td>Significant difference in BCM between groups; no indication of wt loss. Statistical methods used to adjust RMR for weight, height and BCM are not popularly available – hard to judge statistical rigour.</td>
</tr>
<tr>
<td>Macfie (1982) UK</td>
<td>24 Ca 19 MCa 32 Co</td>
<td>Mix – GI Mix – GI + metastatic Normal volunteers + elective surgery WL – 7 ± 5kg WL – 10 ± 5kg WS</td>
<td>No significant difference in slopes of regression lines of REE plotted against TBK for Ca, MCa and Co, but significantly higher intercept in MCa compared to Co (+289 kcal/d)</td>
<td>Co younger than Ca and MCa; TBK significantly lower in MCa.</td>
</tr>
</tbody>
</table>

Ca: cancer; Co: control; GI: gastrointestinal; REE: resting energy expenditure; TBK: total body potassium; TBW: total body water; BCM: body cell mass; MCa: metastatic cancer; WL: weight losing; WS weight stable
<table>
<thead>
<tr>
<th>First Author (Year)</th>
<th>Patient Population</th>
<th>Method</th>
<th>Results</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Arbeit (1984) USA</strong></td>
<td>9 Ca</td>
<td>Mix – sarcoma Mix + metastatic Normal volunteer</td>
<td>WL</td>
<td>REE (IC – VH)</td>
</tr>
<tr>
<td></td>
<td>4 MCa</td>
<td></td>
<td>WL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>11Co</td>
<td></td>
<td>WS</td>
<td></td>
</tr>
<tr>
<td><strong>Lindmark (1984) Sweden</strong></td>
<td>22 WLCa</td>
<td>Mix – GI</td>
<td>WL – 17 ± 2%</td>
<td>REE (IC – VH) TBK (whole body counter)</td>
</tr>
<tr>
<td></td>
<td>6 WSCa</td>
<td>Mix</td>
<td>WS</td>
<td>↑REE (kcal/kg/d) in WLCa, WSCa &amp; WLCo compared to WSCo. Regression lines – plotted against wt&lt;sup&gt;0.75&lt;/sup&gt; – incorrect adjustment for wt, therefore may be over-adjusted. Regression line plotted against TBK – appropriate analysis.</td>
</tr>
<tr>
<td></td>
<td>26 WLCo</td>
<td>Non-cancer patients</td>
<td>WL – 17 ± 2%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>17 WSCo</td>
<td>Controls</td>
<td>WS</td>
<td></td>
</tr>
</tbody>
</table>

Ca: cancer; MCa: metastatic cancer; Co: control; WL: weight losing; WS weight stable; REE: resting energy expenditure; IC: indirect calorimetry; VH: ventilated hood; GI: gastrointestinal; TBK: total body potassium; BW: body weight.
<table>
<thead>
<tr>
<th>First Author (Year)</th>
<th>Place</th>
<th>N (abbrev)</th>
<th>Patient type</th>
<th>Weight status</th>
<th>Method</th>
<th>Results</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hansell (1986) UK</td>
<td></td>
<td>42 WLCa</td>
<td>Mix – GI, lung</td>
<td>WL &gt;10%</td>
<td>REE (IC – VH)</td>
<td>↑ REE (kcal/kgBW/d) in WLCa patients compared to WSCa and WSCo</td>
<td>Significant difference in weight and FFM between groups.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>56 WSCa</td>
<td>Mix – GI</td>
<td>WS</td>
<td>LBM (TBW – tritiated saline)</td>
<td>↓ REE (kcal/kg^0.75/d) in WSCo patients compared to WLCa, WSCa and WLCo.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>16 WLCo</td>
<td>Non cancer patients</td>
<td>WL</td>
<td></td>
<td>No difference in REE between groups when expressed as kcal/kgLBM/d.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>22 WSCo</td>
<td>Non cancer patients</td>
<td>WS</td>
<td></td>
<td>Slope of WLCa regression line significantly steeper than WSCa &amp; WSCo when REE plotted against BW and LBM. Slope of WLCa regression line significantly different than WSCa when REE plotted against wt^0.75.</td>
<td></td>
</tr>
</tbody>
</table>

No significant difference in slope or position of regression lines for all Ca and all Co when REE plotted against LBM. Significant difference in slopes of regression lines for all WL and all WS when REE plotted against LBM.

No significant difference in REE (kcal/kgLBM/d) across tumour types.

Liver metastases – 8 WLCa, 11 WSCa

Patients given 80mL 5% dextrose solution per hour IV for 12 hours prior to test – not true fasting state.

Groups compared by kcal/kgBW/d, kcal/kgLBM/d & kcal/ kg^0.75/d as well as comparing regression lines.

Analysis of regression lines for Ca v's Co, and WL v's WS – appropriate.

Incorrect analysis for comparison of patients with liver metastases & across tumour types – unclear if differences in LBM between groups.

LBM: lean body mass; IV: intravenous.
<table>
<thead>
<tr>
<th>First Author (Year) Place</th>
<th>Patient Population</th>
<th>Method</th>
<th>Results</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peacock (1987) USA</td>
<td>7 WSCa Sarcomas</td>
<td>WS</td>
<td>↑ REE (kcal/d; kcal/kgBCM/d; kcal/m²/d) in WSCa compared to WSCo.</td>
<td>WSCa significantly lower BCM and slightly older than WSCo. Incorrect statistical analysis – adjusted REE per kg BCM and per m²</td>
</tr>
<tr>
<td></td>
<td>6 WSCo Controls – no illnesses or recent surgery</td>
<td>WS &lt;5% wt loss</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>REE (IC – VH) BCM (TBK – whole body counter) BF (4 x SFT) BSA</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Tumour size did not correlate significantly with REE (kcal/m²/d) or BCM.</td>
<td></td>
</tr>
<tr>
<td>Fearon (1988) UK</td>
<td>20 NSCLC</td>
<td>WS n=8 WL n=12 (&gt;5% wt loss)</td>
<td>No significant difference in REE (kJ/kgLBM/d) between all groups (WS and WL NSCLC, WS and WL CR, WS and WL Co).</td>
<td>Incorrect analysis – comparison of groups based on kJ/kgLBM</td>
</tr>
<tr>
<td></td>
<td>CR</td>
<td>WS n=17 WL n=21</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Surgical ward patients</td>
<td>WS n=8 WL n=14</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BF: body fat; SFT: skin fold thickness; BSA: body surface area; NSCLC: non small cell lung cancer; CR: colorectal
<table>
<thead>
<tr>
<th>First Author (Year)</th>
<th>Place</th>
<th>N (abbrev)</th>
<th>Patient type</th>
<th>Weight status</th>
<th>Method</th>
<th>Results</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nixon (1988) USA</td>
<td></td>
<td>45</td>
<td>CR</td>
<td>WL &amp; WS</td>
<td>REE (DC – GLC); FFM (4 x SFT) BSA (Ht/Wt chart)</td>
<td>No difference in REE (kcal/hr; kcal/hr/kgBW; kcal/hr/BSA; kcal/hr/kgFFM) between CR, NSCLC and Co (except anorexia nervosa), according to gender</td>
<td>83% CR &amp; 93% NSCLC patients active metastatic or recurrent disease.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>38</td>
<td>NSCLC</td>
<td>WL &amp; WS</td>
<td></td>
<td></td>
<td>No surgery ≥ 21 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>98 Co</td>
<td>Healthy or non-malignant patients</td>
<td>WS Wt ± 20% IBW</td>
<td></td>
<td></td>
<td>Difference in weight loss between the groups.</td>
</tr>
<tr>
<td>Thomson (1990) South Africa</td>
<td></td>
<td>14 Ca</td>
<td>Oesoph'l</td>
<td>–</td>
<td>REE (IC – MP&amp;NC); FFM (Triceps SFT)</td>
<td>↑ RMR (MJ/d) in Ca males &amp; Ca females compared to Co males &amp; Co females, respectively.</td>
<td>FFM from single skinfold measurement.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>17 Co</td>
<td>Benign disease; age, sex &amp; race matched.</td>
<td>–</td>
<td></td>
<td>No difference in RMR (MJ/kgBW/d; MJ/kgFFM/d) between groups (Ca male &amp; Co male, Ca female &amp; Co female).</td>
<td>Lower wt and triceps skinfold thickness in cancer patients.</td>
</tr>
</tbody>
</table>

DC: direct calorimetry; GLC: gradient layer calorimeter; FFM: fat free mass; Ht: height; Wt: weight; MP&NC: mouthpiece and noseclip.
<table>
<thead>
<tr>
<th>First Author (Year)</th>
<th>Place</th>
<th>N (abbrev)</th>
<th>Patient type</th>
<th>Weight status</th>
<th>Method</th>
<th>Results</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fredrix (1991)</td>
<td>Netherlands</td>
<td>104</td>
<td>GCR</td>
<td>WL – 7%</td>
<td>REE (IC - VH) FFM (BIA) (1/2 GCR patients no measure’t of FFM)</td>
<td>↓ REE (kcal/d) in GCR compared to controls, no difference with GI patients.</td>
<td>GCR patients were significantly older. GCR and GI had significantly lower BMI than Co. No comparison of FFM. Difference in wt loss between groups.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>32 GI</td>
<td>Non- malignant GI disease</td>
<td>WL – 4%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>40 Co</td>
<td>Healthy</td>
<td>WS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fredrix (1991)</td>
<td>Netherlands</td>
<td>104</td>
<td>GCR</td>
<td>WL – 7%</td>
<td>REE (IC - VH) FFM (BIA) (1/2 GCR patients no measure’t of FFM)</td>
<td>↑ REE (kcal/kgBW/d; kcal/kgFFM/d) in NSCLC compared with GCR and Co.</td>
<td>GCR cancer patients were older. Significant difference in FFM and wt loss between groups.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>47</td>
<td>NSCLC</td>
<td>WL – 7%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>40 Co</td>
<td>Healthy</td>
<td>WS</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

GCR: gastric and colorectal; BIA: bioelectrical impedance analysis; BMI: body mass index
<table>
<thead>
<tr>
<th>First Author (Year)</th>
<th>Place</th>
<th>N (abbrev)</th>
<th>Patient Population</th>
<th>Method</th>
<th>Results</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fredrix (1991)</td>
<td>Netherlands</td>
<td>30</td>
<td>NSCLC</td>
<td>WL n=17 (&gt; 5% wt loss) WS n=13</td>
<td>REE (IC – VH) FFM (BIA)</td>
<td>↑ REE (kcal/kgBW/d, kcal/kgFFM/d) in WL compared to WS patients</td>
</tr>
<tr>
<td>Hyltander (1991)</td>
<td>Sweden</td>
<td>81 WLCa 25 WSCa</td>
<td>Mix – GI Mix – testes, GI</td>
<td>WL 16kg±1% WS</td>
<td>REE (IC – VH) (2 different machines used) TBK (Whole body counter)</td>
<td>↑ REE (kcal/d; kcal/kgBW/d; kcal/m²/d) in WLCa vs WLCa; and WSCa vs WSCa. ↑ REE (kcal/TBK/d) in WLCa vs WLCa.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>51 WLCa 45 WSCa</td>
<td>Patients – same ward Patients – same ward</td>
<td>WL – 13kg ±1% WS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Falconer (1994)</td>
<td>UK</td>
<td>21Ca 16Co</td>
<td>Pancreatic Patients – minor elective surgery</td>
<td>WL WS</td>
<td>REE (IC – VH) FFM &amp; BCM (BIA)</td>
<td>↑ REE (kcal/kgBW/d; kcal/kgFFM/d; kcal/kgBCM/d) in Ca compared with Co ↑ REE (kcal/kgBW/d; kcal/kgFFM/d; kcal/kgBCM/d) in Ca with APPR (CRP&gt;10mg/L) compared to Ca without. (No significant difference in wt, FFM &amp; BCM between groups)</td>
</tr>
<tr>
<td>First Author (Year)</td>
<td>Place</td>
<td>N (abbrev)</td>
<td>Patient type</td>
<td>Weight status</td>
<td>Method</td>
<td>Results</td>
</tr>
<tr>
<td>---------------------</td>
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</tr>
<tr>
<td>Staal-van den Brekel (1994) Netherlands</td>
<td>17 83</td>
<td>SCLC NSCLC</td>
<td>WS n=70 WL n=30 (≥10% wt loss)</td>
<td>REE (IC - VH) FFM (BIA – estimated from cancer specific equations)</td>
<td>No difference in REE (kcal/d; kcal/kgFFM/d) between WL and WS. ↑REE (kcal/kgBW/d) in WL compared to WS. ↑REE (kcal/kgFFM/d) in SCLC compared to NSCLC, and in patients with central tumour localization compared to patients with peripheral tumour localization.</td>
<td>No control group – compared WL and WS cancer patients.</td>
</tr>
<tr>
<td>Staal-van den Brekel (1995) Netherlands</td>
<td>87</td>
<td>NSCLC</td>
<td>WS n=61 WL n=26 (≥10% wt loss)</td>
<td>REE (IC - VH)</td>
<td>↑REE (REE&lt;sub&gt;m&lt;/sub&gt;/REE&lt;sub&gt;p&lt;/sub&gt;) in WL compared to WS. Tumour stage significantly differed between WL and WS</td>
<td>No control group. Incorrect analysis – compared groups based on REE&lt;sub&gt;m&lt;/sub&gt;/REE&lt;sub&gt;p&lt;/sub&gt;.</td>
</tr>
<tr>
<td>Staal-van den Brekel (1997) Netherlands</td>
<td>33 33</td>
<td>SCLC NSCLC</td>
<td>WS n=23 WL n=10 (≥10% wt loss)</td>
<td>REE (IC - VH) FFM (BIA)</td>
<td>↑REE adjusted for FFM in SCLC &amp; NSCLC patients compared to Co. ↑REE adjusted for FFM in SCLC compared to NSCLC.</td>
<td>Groups matched for age, sex and FFM. Co was wt stable, but 10 SCLC and 11 NSCLC cancer patients had lost ≥10% wt.</td>
</tr>
<tr>
<td>33 Co Healthy</td>
<td>WS</td>
<td></td>
<td></td>
<td></td>
<td>Tumour stage did not influence metabolic parameters in SCLC patients.</td>
<td>ANCOVA used to make adjustments – appropriate.</td>
</tr>
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</table>

SCLC: small cell lung cancer; REE<sub>p</sub>: predicted REE; ANCOVA: analysis of covariance
<table>
<thead>
<tr>
<th>First Author (Year)</th>
<th>Place</th>
<th>Patient Population</th>
<th>Method</th>
<th>Results</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jatoi (1999) USA</td>
<td>17 Co</td>
<td>NSCLC</td>
<td>WL &gt;5% (n=4) WS (n=13)</td>
<td>REE (IC – VH)</td>
<td>No significant difference in mean REE (kcal/d) between NSCLC &amp; Co. No significant difference in BMI between groups but no indication of weight or FFM.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Healthy –sex, age (± 5 yrs) and BMI (± 3 kg/m²)</td>
<td>–</td>
<td>–</td>
<td>&gt;5% wt loss in past 6 months in some cancer patients. Absolute REE compared to that of matched control – no range provided for comparing REE between matched individuals – extreme definition for hyper- and hypometabolic.</td>
</tr>
<tr>
<td>Barber (2000) UK</td>
<td>16 Ca</td>
<td>Pancreatic</td>
<td>WL 17.7%</td>
<td>REE (IC – VH) LBM &amp; BCM (BIA)</td>
<td>No significant difference in REE (kcal/d) between Ca and Co. Ca significantly lower weight than Co. Ca had severe WL compared to WS Co. No comparison of LBM between groups.</td>
</tr>
<tr>
<td></td>
<td>6 Co</td>
<td>Healthy</td>
<td>WS</td>
<td>↑ REE (kcal/kgBW/d; kcal/kgLBM/d; kcal/kgBCM/d) in Ca compared to Co. Incorrect analysis – compared groups based on kcal/kgBW/d, kcal/kgLBM/d &amp; kcal/kgBCM/d.</td>
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### Table C.1 Continued

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<th>Method</th>
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</thead>
<tbody>
<tr>
<td>Bosaeus (2001) Sweden</td>
<td></td>
<td>Mix – GI</td>
<td>REE&lt;sub&gt;n&lt;/sub&gt; (IC - VH)</td>
<td>No difference in REE (kcal/kgBW/d) across tumour types or between men &amp; women.</td>
<td>Heterogeneous group – cancer type, wt status. No control group – based on tumour types and weight status. Incorrect analysis – compared groups based on kcal/kgBW/d.</td>
</tr>
<tr>
<td>Jatoi (2001) USA</td>
<td>USA</td>
<td>NSCLC</td>
<td>REE (IC - VH)</td>
<td>No difference in REE (kcal/d, kcal/TBW) between NSCLC and Co.</td>
<td>Groups matched for gender, age, BMI. No difference in LBM, BCM or TBW. ANCOVA used to make adjustments – appropriate.</td>
</tr>
<tr>
<td>Scott (2001) UK</td>
<td></td>
<td>NSCLC</td>
<td>REE (IC - VH)</td>
<td>No significant difference in REE (kcal/kgBW/d) between NSCLC &amp; Co.</td>
<td>All males. Co were significantly younger than NSCLC. Slightly lower TBK in NSCLC. Incorrect analysis – compared groups based on kcal/d, kcal/kgBW/d &amp; kcal/mmolK/d.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Healthy</td>
<td>TBK (whole body counter)</td>
<td>↑ REE (kcal/kgBW/d) in patients with severe wt loss (&gt;10% wt loss) compared to wt stable patients and underweight patients compared to normal weight patients.</td>
<td></td>
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<tr>
<td></td>
<td>Co</td>
<td>Control</td>
<td>–</td>
<td>↑ REE in cancer patients compared to controls when REE adjusted for LBM and when REE adjusted for BCM.</td>
<td></td>
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<tr>
<td>First Author (Year)</td>
<td>Place</td>
<td>N</td>
<td>Patient Types</td>
<td>Weight Status</td>
<td>Method</td>
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<tr>
<td>Knox (1983) USA</td>
<td></td>
<td>200</td>
<td>Mix – GI, Gyn</td>
<td>90 ± 11% UBW</td>
<td>REEm (IC – MP&amp;NC)</td>
</tr>
</tbody>
</table>
|                     |       |     |               |               | REEp (HBE) | 26% patients hypermetabolic (> 110% REEp)  
41% patients normometabolic (90-110% REEp)  
33% patients hypometabolic (< 90% REEp) | Only excluded patients < 5 days post-operative |
|                     |       |     |               |               |         | Hypermetabolic patients were older and lower %IBW than normo- or hypo-metabolic patients. |
|                     |       |     |               |               |         | No correlation between duration of disease & REE (%REEp). No difference between metabolic groups for % patients with liver metastases, or tumour burden. |
| Dempsey (1984) USA  |       | 173 | GI            | WL 13%        | REEm (IC – MP&NC) | Mean REEm was 97.9% of REEp for the group – no significant difference. | Different conditions for measuring REE – measurements taken more than 2 hours after previous meal |
|                     |       |     |               |               | REEp (HBE) | 22% patients hypermetabolic (> 110% REEp)  
42% patients normometabolic (90-110% REEp)  
36% patients hypometabolic (< 90% REEp) | |
|                     |       |     |               |               |         | No significant differences in tumour burden, disease duration or % patients with liver metastases between groups. Largest proportion oesophageal & colorectal cancer patients – normometabolic; pancreatic & hepatobiliary tumours – hypometabolic; gastric cancer – hypermetabolic. |

GI: gastrointestinal; UBW: usual body weight; REEm: measured resting energy expenditure; IC: indirect calorimeter; MP&NC: mouthpiece and noseclip; REEp: predicted resting energy expenditure; HBE: Harris-Benedict equations
<table>
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<th>Patient Population</th>
<th>Method</th>
<th>Results</th>
<th>Comment</th>
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<tr>
<td>Lindmark (1984)</td>
<td>Sweden</td>
<td>REE&lt;sub&gt;m&lt;/sub&gt; (IC – VH)</td>
<td>↑ REE&lt;sub&gt;m&lt;/sub&gt; in WL compared to REE&lt;sub&gt;p&lt;/sub&gt;. Mean REE&lt;sub&gt;m&lt;/sub&gt; was 108% of REE&lt;sub&gt;p&lt;/sub&gt; for WL group.</td>
<td>REE of WS controls is overestimated by Harris-Benedict equation.</td>
</tr>
<tr>
<td>22</td>
<td>Mix – GI</td>
<td>WS</td>
<td>REE&lt;sub&gt;p&lt;/sub&gt; (HBE)</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Mix</td>
<td>WL 17 ± 2%</td>
<td>No significant difference between mean REE&lt;sub&gt;m&lt;/sub&gt; and mean REE&lt;sub&gt;p&lt;/sub&gt; for WS group (99.6% of REE&lt;sub&gt;p&lt;/sub&gt;).</td>
<td></td>
</tr>
<tr>
<td>Merrick (1988)</td>
<td>USA</td>
<td>REE&lt;sub&gt;m&lt;/sub&gt; (IC – VH)</td>
<td>No significant difference between mean REE&lt;sub&gt;m&lt;/sub&gt; and mean REE&lt;sub&gt;p&lt;/sub&gt; for group (kcal/kg).</td>
<td>Some patients receiving 5% glucose infusions, 11 with liver metastases</td>
</tr>
<tr>
<td>21</td>
<td>CR</td>
<td>WS &amp; WL Weight loss in some patients (2.7 – 15.5kg)</td>
<td></td>
<td>REE&lt;sub&gt;m&lt;/sub&gt; and REE&lt;sub&gt;p&lt;/sub&gt; expressed as kcal/kg.</td>
</tr>
<tr>
<td>68</td>
<td>Mix – GI, CR</td>
<td>REE&lt;sub&gt;m&lt;/sub&gt; (IC – VH)</td>
<td>34% patients hypermetabolic (&gt; 110% REE&lt;sub&gt;p&lt;/sub&gt;)</td>
<td></td>
</tr>
<tr>
<td>104</td>
<td>GCR</td>
<td>REE&lt;sub&gt;p&lt;/sub&gt; (HBE)</td>
<td>51% patients normometabolic (90-110% REE&lt;sub&gt;p&lt;/sub&gt;)</td>
<td></td>
</tr>
<tr>
<td>15% patients hypometabolic (&lt; 90% REE&lt;sub&gt;p&lt;/sub&gt;)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fredrix (1991)</td>
<td>Netherlands</td>
<td>REE&lt;sub&gt;m&lt;/sub&gt; (IC – VH)</td>
<td>Mean REE&lt;sub&gt;m&lt;/sub&gt; was 103.9±9.8% of REE&lt;sub&gt;p&lt;/sub&gt; for GCR</td>
<td>Hypermetabolic classed as &gt; 115% REE&lt;sub&gt;p&lt;/sub&gt;.</td>
</tr>
<tr>
<td>30</td>
<td>NSCLC</td>
<td>REE&lt;sub&gt;p&lt;/sub&gt; (HBE)</td>
<td>13% GCR patients hypermetabolic (≥115% REE&lt;sub&gt;p&lt;/sub&gt;)</td>
<td>96 patients GI surgery</td>
</tr>
<tr>
<td>104</td>
<td>WL 7 ± 6%</td>
<td>REE&lt;sub&gt;m&lt;/sub&gt; (IC – VH)</td>
<td>60% of patients hypermetabolic (≥115% REE&lt;sub&gt;p&lt;/sub&gt;)</td>
<td>25 patients liver metastases</td>
</tr>
<tr>
<td>30</td>
<td>WL 6 ± 7%</td>
<td>REE&lt;sub&gt;p&lt;/sub&gt; (HBE)</td>
<td>Mean REE&lt;sub&gt;m&lt;/sub&gt; was 120 ± 13% of REE&lt;sub&gt;p&lt;/sub&gt;.</td>
<td>Hypermetabolic classed as &gt; 115% REE&lt;sub&gt;p&lt;/sub&gt;.</td>
</tr>
</tbody>
</table>

WL: weight losing; WS: weight stable; VH: ventilated hood; CR: colorectal; GCR: gastric and colorectal; NSCLC: non small cell lung cancer
<table>
<thead>
<tr>
<th>First Author (Year)</th>
<th>Patient Population</th>
<th>Method</th>
<th>Results</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hyltander (1991) Sweden</strong></td>
<td>81 Mix – GI, 25 Mix – testes, GI</td>
<td>REE&lt;sub&gt;m&lt;/sub&gt; (IC – VH) (2 different machines used) REEP (HBE)</td>
<td>No significant difference between REE&lt;sub&gt;m&lt;/sub&gt; and REEP in WL (103% of REEP) RREE&lt;sub&gt;m&lt;/sub&gt; lower than REEP in WS. Mean REE&lt;sub&gt;m&lt;/sub&gt; was 96.6% of REEP for WS</td>
<td>Weight loss defined as &gt;4% weight loss of UBW during recent 6 months. REE of WS &amp; WL controls is overestimated by HBE.</td>
</tr>
<tr>
<td><strong>Staal-van den Brekel (1994) Netherlands</strong></td>
<td>100 SCLC (17), NSCLC (83)</td>
<td>REE&lt;sub&gt;m&lt;/sub&gt; (IC – VH) REEP (HBE)</td>
<td>↑ RREE&lt;sub&gt;m&lt;/sub&gt;/REE&lt;sub&gt;p&lt;/sub&gt; in WL group compared to WS group – 123 ± 12 vs 115 ± 13 %REE&lt;sub&gt;p&lt;/sub&gt; 74% patients hypermetabolic (≥110% REEP).</td>
<td>WL defined as ≥10% wt loss</td>
</tr>
<tr>
<td><strong>Staal-van den Brekel (1995) Netherlands</strong></td>
<td>87 NSCLC</td>
<td>REE&lt;sub&gt;m&lt;/sub&gt; (IC – VH) REEP (HBE)</td>
<td>Mean REE&lt;sub&gt;m&lt;/sub&gt; was 118 ± 12% of REEP for the group 77% patients hypermetabolic (≥110% REEP) 23% patients normo- or hypometabolic (&lt;110% REEP)</td>
<td>WL defined as ≥10% wt loss</td>
</tr>
<tr>
<td><strong>Staal-van den Brekel (1997) Netherlands</strong></td>
<td>33 SCLC, 33 NSCLC</td>
<td>REE&lt;sub&gt;m&lt;/sub&gt; (IC – VH) REEP (HBE)</td>
<td>Mean REE&lt;sub&gt;m&lt;/sub&gt; was 124 ± 14% of REEP for SCLC Mean REE&lt;sub&gt;m&lt;/sub&gt; was 116 ± 14% of REEP for NSCLC</td>
<td>All subjects matched for sex, age and FFM</td>
</tr>
</tbody>
</table>

### Table C.2 Continued

<table>
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<tr>
<th>First Author (Year)</th>
<th>Patient Population</th>
<th>Method</th>
<th>Results</th>
<th>Comment</th>
</tr>
</thead>
</table>
| **Bosaeus (2001)** Sweden | 297 Mix – GI | REE<sub>m</sub> (IC – VH) | Mean REE<sub>m</sub> was 112 ± 14% of REE<sub>p</sub>  
No difference in %REE<sub>p</sub> across tumour types. | Large variation in weight loss |
| | WL >10% (n=127); WL 5-10% (n= 71); WS (n=85); WG (n=14) | REE<sub>p</sub> (HBE) | 48.5% patients hypermetabolic (>110% REE<sub>p</sub>)  
50.2% patients normometabolic (90 - 110% REE<sub>p</sub>)  
1.4% patients hypometabolic (< 90% REE<sub>p</sub>) | |
| **Scott (2001)** UK | 23 NSCLC WS | REE<sub>m</sub> (IC – VH) | ↑ Mean REE<sub>m</sub> compared to REE<sub>p</sub> in cancer patients (104 (93 – 125)%).  
87% patients hypermetabolic (>110% REE<sub>p</sub>) | |
| | | REE<sub>p</sub> (HBE) | | |
| **Bauer (2004)** Australia | 8 Pancreatic WL >5% in 6 months | REE<sub>m</sub> (IC – MP&NC) | Mean REE<sub>m</sub> was 101% of REE<sub>p</sub>.  
20% patients hypermetabolic (> 110% REE<sub>p</sub>)  
60% patients normometabolic (90-110% REE<sub>p</sub>)  
20% patients hypometabolic (< 90% REE<sub>p</sub>) | Repeated measurements on 4 patients (total of 15 measurements).  
Receiving different forms of palliative treatment. |

**WG:** weight gain
Appendix D: Information Package and Consent Forms (Phase 2)
PARTICIPANT INFORMATION PACKAGE

Project Title: The prescription of energy requirements for people with cancer

Chief Investigators: Ms Marina Reeves
PhD Candidate, Centre for Health Research
Queensland University of Technology

Professor Sandra Capra
Director, Australian Centre for Evidence Based Nutrition & Dietetics
University of Newcastle

Ms Judy Bauer
Nutrition Services Manager
The Wesley Hospital

Associate Professor Peter Davies
Director, Children’s Nutrition Research Centre
University of Queensland

Dr Diana Battistutta
Biostatistician, School of Public Health
University of Wollongong

This research study is being conducted as part of a Doctor of Philosophy degree at Queensland University of Technology (School of Public Health) and will be performed by Marina Reeves under the guidance of Professor Sandra Capra, Associate Professor Peter Davies and Dr Diana Battistutta and Ms Judy Bauer. This information package gives you details about the study. Please read it carefully and take your time before deciding whether to take part. Please discuss anything you don’t understand with your doctor and/or one of the investigators.

Why is this research being carried out?

Many patients with cancer lose weight due to changes in the amount of energy the body uses. Doctors and dietitians try to stop this weight loss by giving patients extra food in various forms. This study will assist in determining how much food patients with cancer need to meet their body’s requirements, so better nutrition treatment may be offered.

People who do not have cancer, of similar sex, age, ethnicity, weight and height to that of cancer patients, will also be involved in the study, to see whether there are differences in the body’s energy needs between people with cancer and people without cancer.
What does the study involve?

You will need to fast overnight (for 12 hours) and will have measurements conducted early in the morning (starting between 7-9am). You will have to come to The Wesley Hospital to have measurements conducted. At this visit you will have a number of non-invasive measurements conducted using standard techniques, as described below.

Schedule for testing:

1. Rest quietly (30 mins)
2. Your energy expenditure will be measured while lying quietly using two standard instruments:
   a) Method 1 – Mouthpiece and noseclip (30 mins)
   b) Method 2 – Facemask or Mouthpiece and noseclip (15 mins)
   These instruments measure the air you breathe. Measurements with the two instruments may be conducted in reverse order.
3. Weight and height will be measured and information on your recent weight history will be collected (5 mins)
4. The amount of muscle and fat in your body will be measured on a standard machine (5mins)*
5. Your nutritional status will be assessed by a number of questions and a physical assessment of body fat and muscle stores (5 mins)

* You will not be able to undergo Step 4 if you have a pacemaker.

For patients with cancer, additional information relating to your medical history that is relevant to the study will be required. If you give permission for the chief investigators to access your medical record this information can be collected.

How will taking part in the study help me and are there any risks?

You will have been asked to take part in this study because we think you can help us. Involvement in the study will not include any form of treatment but you are welcome to have a copy of your results from the various tests. The study may result in improved nutrition care for patients with cancer.

The measurements taken during this study are not harmful in any way. All the tests to be performed are non-invasive. Each test will be carried out by a trained dietitian.

Confidentiality

Your identity will always be treated as confidential and will not be disclosed to the public. For patients with cancer, your doctor will be told that you are taking part in the study and hospital notes will state that you are in this study. If results of this research study are published, your identity will remain
confidential and any reference to individual results will relate only to your study number.

You can change your mind even if you agree to take part

Participation in this study is entirely voluntary. Before starting you will be asked to consent in writing. However, by signing this form you are not waiving any of your legal rights. If at any time you feel that you do not wish to continue, you may withdraw from the study and this will not affect your future care by your doctor or hospital in any way.

Any further questions or concerns

If you have any further questions about the study you may contact me on 3864 5853, or my supervisor, Associate Professor Peter Davies, on 3636 3765. If you have any concerns about the ethical conduct of the study you may contact the Secretary of the QUT Human Research Ethics Committee on 3864 2902, or The Wesley Hospital Ethics Committee on 3232 7926.

Thank you for your consideration of participation in this study. Your help is greatly appreciated in the completion of my Doctor of Philosophy degree. Please ensure that you have read and understood the previous information.

Thank you for your assistance.

Marina Reeves APD  
PhD Candidate
Agreement to Provide Contact Details to Chief Investigator of Study
“The Prescription of Energy Requirements for People with Cancer”

I consent to my contact details (name and phone number) being provided to Marina Reeves (Chief Investigator) for further discussion of participation in the above-mentioned study.

Signed .............................................................. Date ................................

Name (Print)

......................................................................

Contact Phone Number

......................................................................

Witness ......................................................... Date ................................
The Prescription of Energy Requirements for People with Cancer

CONSENT FORM

Study Agreement:

Have you read the information package about this study? YES/NO

Have you been able to ask questions about this study? YES/NO

Have you received answers to all your questions? YES/NO

Have you received enough information about this study? YES/NO

Do you understand that you are free to withdraw from this study?

At any time

Without giving a reason for withdrawing

Without affecting your future medical care YES/NO

For Patients: Do you agree to your study related health records (including your medical record) being reviewed by members of the research team or The Wesley Hospital Multidisciplinary Ethics Committee? YES/NO

Do you agree to participate in the project? YES/NO

Signed .............................................................. Date .........................

Name (Block letters)
...........................................................................................................

Investigator .............................................................. Date .........................

Witness .............................................................. Date

..................................................
Would you like to know your metabolic rate?
(ie how many calories/kilojoules you expend)

As part of a PhD research project we are looking for any interested “healthy” volunteers who would like to find out their metabolic rate.

Are you or your spouse/partner/family member/friend:
- Male, 36 - 77yrs, height 158 - 193 cm & weight 67 - 100 kg? or
- Female, 47 - 73yrs, height 144 - 180 cm & weight 47 - 67 kg?

Involvement in this study will help us to:
- better understand the energy requirements of people with cancer (by comparing to healthy people).
- validate a new, quick and easy device for measuring metabolic rate.

What is involved?
All we ask for is 1.5 - 2 hours of your time one morning (we will even supply you with breakfast)!

- You will have your energy expenditure measured by 2 different methods (these methods measure your breathing ie how much oxygen you consume and carbon dioxide you produce).
- Information on your weight, height, weight history, body composition and nutritional status will be collected.

At the end you will know your metabolic rate which will help you if you are wanting to lose or gain weight or simply if you are interested in your health.

If you or anyone you know fits these criteria, or for more information please contact Marina Reeves on 3864 5853 or m.reeves@qut.edu.au
Appendix E: Data Collection Forms (Phase 2)
### Data Collection Form (A)

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<tr>
<th>Sex: M / F</th>
<th>Smoker:</th>
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#### Nutritional Assessment

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**Weight History:**
- Weight loss
  - Intentional
  - Unintentional

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<th>% Body Fat:</th>
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<th>PG-SGA:</th>
<th>SGA:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tbody>
</table>

#### Energy Expenditure

<table>
<thead>
<tr>
<th>VMax 229</th>
<th>MedGem</th>
</tr>
</thead>
<tbody>
<tr>
<td>Order 1</td>
<td>Order 1</td>
</tr>
<tr>
<td>Order 2</td>
<td>Order 2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>VO2</th>
<th>VO2</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>VCO2</th>
<th>VCO2</th>
<th>REE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N/A</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>RQ</th>
<th>RQ</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Constant (0.85)</td>
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</table>

<table>
<thead>
<tr>
<th>REE</th>
<th>REE</th>
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</table>

#### Prediction Equations

<table>
<thead>
<tr>
<th>Harris-Benedict</th>
<th>Owen et al</th>
</tr>
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<tr>
<td></td>
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<table>
<thead>
<tr>
<th>Schofield</th>
<th>Mifflin et al</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Data Collection Form (B)</strong></td>
<td></td>
</tr>
<tr>
<td>-----------------------------</td>
<td></td>
</tr>
<tr>
<td><strong>Study ID:</strong></td>
<td><strong>Age:</strong></td>
</tr>
<tr>
<td><strong>Sex:</strong></td>
<td><strong>Oncologist:</strong></td>
</tr>
</tbody>
</table>

### Medical History

- **Tumour type**
- **Stage**
  - (T,N,M)
- **Metastases**
  - [ ] No
  - [ ] Yes
- **Prognosis**
- **Recurrence**
  - [ ] No
  - [ ] Yes

### Treatment:

- [ ] XRT
  - [ ] Pre-XRT
  - [ ] Mid XRT
  - [ ] <4 wks
  - # planned .........
  - # complete .........
  - Gray .............

- [ ] CTx
  - [ ] Pre-CTx
  - [ ] Current
  - [ ] <4wks
  - >4wks
  - # planned .........
  - # complete .........

- [ ] Sx
  - Post-XRT
  - [ ] Complete
  - [ ] Incomplete
  - .........

### General Medical History:

- [ ] Febrile
- [ ] Oedema

### Medications:

- [ ] Steroids
### Data Collection Form - Healthy

<table>
<thead>
<tr>
<th>Study ID:</th>
<th>Age:</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
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</tbody>
</table>

| Sex: | Smoker: |
| M / F |        |

#### Nutritional Assessment

<table>
<thead>
<tr>
<th>Weight:</th>
<th>Height:</th>
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</thead>
<tbody>
<tr>
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</tbody>
</table>

**Weight History:**
- [ ] Weight loss
  - [ ] Intentional
  - [ ] Unintentional

<table>
<thead>
<tr>
<th>BMI:</th>
<th>FFM:</th>
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<table>
<thead>
<tr>
<th>% Body Fat:</th>
<th>TBW:</th>
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<tr>
<td></td>
<td>Impedance</td>
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<td></td>
<td>1 2</td>
<td>1 2</td>
</tr>
<tr>
<td>VO2</td>
<td></td>
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</tr>
<tr>
<td>VCO2</td>
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Data Collection Form (Healthy) – Version 1, February 2003
REFERENCES


Branson RD. The measurement of energy expenditure: instrumentation, practical considerations, and clinical application. Respiratory Care 1990;35:640-659.


Case KO, Brahler CJ, Heiss C. Resting energy expenditures in Asian women measured by indirect calorimetry are lower than expenditures calculated from prediction equations. Journal of the American Dietetic Association 1997;97:1288-1292.


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