COST EFFECTIVENESS ANALYSIS OF ERYTHROPOIETIN THERAPY IN THE MINISTRY OF HEALTH DIALYSIS PROGRAMME

by

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Thesis submitted in fulfilment of the
requirements for the degree
of Doctor of Philosophy

JUNE 2006

ACKNOWLEDGEMENTS

I am grateful to Dr. Lim Teck Onn, Head of Clinical Research Centre of Hospital Kuala Lumpur and Associate Professor Dr. Mohamed Izham Mohamed Ibrahim for their supervision and expert help in academic writing.

I am particularly indebted to Mr. Adrian Goh of Clinical Research Centre for his invaluable assistance and advice. My thanks also go to Miss Noor Zakiah Ghazali and Mr. Abu Bakar Mansor for their help in collecting most of the time trade-off exercise data. The nursing staff of the dialysis centers, who collected some of the data, is gratefully acknowledged for their assistance.

Special appreciation to Miss Noor Zakiah for helping me in getting my thesis done till the end. I would like to express my gratitude to Professor Paul Kind of the University of York, UK for his expert advice in the quality of life instrument.

I am profoundly grateful to my beloved husband, Mr. Mansor Man for his moral support, encouragement and impeccable patience. This thesis is dedicated to my children, Faiz Najmi, Faris Aiman, Farhan Nizar and Maisarah Najla.

I wish to thank my sponsor, the Public Services Department for providing me the full-paid leave throughout my research term. This work was also supported by the grant from the Medium Research Grant (MRG-2003-7) of Ministry of Health, Malaysia and I must thank the committee for this support.

Last but not least, my sincere thanks to Dato' Dr. Zaki Morad Mohd. Zaher and all the nephrologists who are involve in this project and those whom have helped me in one way or another.

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GLOSSARY

Cost Effectiveness Analysis

A technique in which the cost and effects of an intervention and an alternative are presented in a ratio of incremental cost to incremental effect.

Cost Effectiveness Ratio

The incremental cost of using an intervention to obtain a unit of effectiveness (such as dollars per life-year gained) compared with an alternative such as another treatment or no treatment.

Discounting

The process of finding the present worth of a future amount of money. Generally this expression is obtained in the form of a discount factor from a set of compounding and discounting tables. The underlying concept is sometimes referred to as the time value of money. The conversion of future dollars spent and future health outcomes (such as life years saved in 20 years from an intervention today) to their present value.

End stage renal disease / failure

Severe kidney disease or chronic kidney failure that has reduced the kidney function to 10 percent or less of normal function, requiring the patient to have either dialysis or a transplant in order to live. Also called renal failure.

Incremental Cost Effectiveness Ratio

The incremental cost of an intervention divided by the incremental effectiveness.

Sensitivity Analysis

Analyses that determine the impact of changing one or several variables in a model or analysis on the outcome of the analysis. A sensitivity analysis allows a range of plausible inputs to be considered when there is uncertainty about the true value of an input. An example is comparing results using a discount rate of 3% with result using rates of 5% and 10%.

Shadow Price

The social opportunity cost of an outcome.

Time Trade-Off

A method for assessing preferences for a given health state, in which the respondent is asked how much time he or she would be willing to trade from a given lifespan in the health state, to have the remaining lifespan in perfect health. For example, a respondent might have a 40 year life expectancy in a given health state, and might be willing to trade 10 years in order to have a 30 year life expectancy in perfect health.

Quality-Adjusted Life Years (QALYs)

A method that assigns a preference weight to each health state, determines the time spent in each state, and estimates life-expectancy as the sum of the products of each preference weight and time spent for each state.

Quality of Life (QOL)

An individual's overall sense of well-being. In medical studies, quality of life is measured using various standardized questionnaires to rate such factors as pain, mood, energy level, family and social interactions, sexual function, ability to work, and ability to keep up with routine daily activities.

Weights

The numerical score associated with the value attached to a given health state. Scores typically range between 1.0 for perfect health and 0.0 for dead (some studies have estimated values less than 0 for health states considered worse than dead).

ABBREVIATIONS

BMI	Body Mass Index
CAPD	Continuous Ambulatory Peritoneal Dialysis
CCF	Congestive Cardiac Failure
CEA	Cost Effectiveness Analysis
CER	Cost Effectiveness Ratio
Cerebro VD	Cerebro Vascular Disease
CI	Confidence interval
CRC	Clinical Research Centre
CRF	Case Report Form
CRP	C-Reactive Protein
CVD	Cardio Vascular Disease
CUA	Cost Utility Analysis
DM	Diabetes Mellitus
EPO	Erythropoietin
EQ-5D	EuroQoL 5 Dimension
ESRD	End-Stage Renal Disease
ESRF	End-Stage Renal Failure
g/dl	Gram per decilitre
GBP	Pounds sterling
HB	Haemoglobin
HD	Haemodialysis
HKL	Hospital Kuala Lumpur
HPT	Hypertension
HYE	Healthy-Years Equivalents
ICER	Incremental Cost Effectiveness Ratio
ID	Identification
IHD	Ischemic Heart Disease
LE	Life Expectancy
LYS	Life Year Saved
MOH	Ministry of Health
MRG	Major Research Grant
NGO	Non-Government Organisation
NKF-DOQI	National Kidney Foundation's Dialysis Outcomes Quality Initiative
NRR	National Renal Registry
PD	Peritoneal Dialysis
QALY	Quality-Adjusted Life Year
QLI	Quality of Life Index
QOL	Quality of life
RM	Ringgit Malaysia
SD	Standard Deviation
TTO	Time Trade-Off
U/week	Units per Week
UK	United Kingdom
US	United States
USA	United States of America
USD	United States Dollar
VAS	Visual Analogue Scale

ANALISIS KEBERKESANAN KOS TERAPI ERITROPOEITIN DALAM PROGRAM DIALISIS KEMENTERIAN KESIHATAN MALAYSIA

ABSTRAK

Kekurangan darah bagi pesakit yang mengalami kegagalan buah pinggang pada peringkat akhir adalah disebabkan oleh buah pinggang tidak dapat berfungsi untuk mengeluarkan eritropoietin (EPO) endogenus. Eritropoietin adalah sejenis ubat yang mahal tetapi berguna kepada pesakit-pesakit yang mengalami kekurangan darah termasuk penyakit barah dan talassemia. Oleh kerana banyak pesakit mengalami kekurangan darah dalam pelbagai jenis penyakit, maka penggunaan EPO sangat tinggi. Ini menyebabkan peningkatan ketara dalam bajet kerajaan. Objektif-objektif kajian ini adalah untuk menentukan jangkaan hidup, peningkatan dalam tahap hemoglobin bagi pesakit anemia yang berkaitan dengan terapi EPO, peningkatan dalam cara hidup berkualiti yang berkaitan dengan hemoglobin, indeks utiliti, kos tambahan yang diperlukan untuk EPO serta keberkesanan kos bagi program dialisis Kementerian Kesihatan Malaysia, yang diukur dengan kos per *quality-adjusted life year* (QALY). Kaedah yang digunakan untuk soalan-soalan cara hidup berkualiti yang bersangkutan dengan kesihatan adalah EQ-5D dan Indeks Spitzer serta tatacara *time trade-off* (TTO). Nilai kos yang digunapakai ditetapkan dalam Ringgit Malaysia bagi tahun 2004. Pangkalan data untuk Registri Pesakit Buah Pinggang Kebangsaan bagi tahun 1997 hingga 2004 digunakan sebagai asas pemilihan pesakit dalam kajian ini dan data ini digunakan apabila maklumat yang diperlukan tidak didapati untuk memenuhi tujuan kajian ini.

Terapi menggunakan EPO dapat meningkatkan purata tahap hemoglobin bagi pesakit hemodialisis yang kekurangan darah sebanyak 9.39 % (8.96 g/dl hingga ke 9.81 g/dl) manakala 8.48 % (8.96 g/dl hingga ke 9.72 g/dl) untuk pesakit *continuous ambulatory peritoneal dialysis* (CAPD) pada tahap permulaan hemoglobin di antara 8 dan 10 g/dl. Purata preskripsi dosej EPO pada permulaan tahap hemoglobin yang sama adalah 4679 U seminggu untuk pesakit hemodialisis dan 4477 U seminggu untuk pesakit CAPD. Purata kos untuk meningkatkan 1 g/dl hemoglobin dalam setahun adalah RM5274 untuk pesakit hemodialisis dan RM4887 untuk pesakit CAPD bagi tahap permulaan hemoglobin yang sama.

Keseluruhannya, jangkaan hidup bagi pesakit dialisis adalah 10.13 tahun dengan hayat kehidupan hemodialisis lebih panjang (11.37 tahun) daripada CAPD (7.94 tahun). Petanda-petanda untuk jangkaan hidup adalah umur pada permulaan rawatan dialisis, kencing manis, tahap hemoglobin, paras albumin dan jenis rawatan dialisis. Indeks untuk hidup berkualiti bagi pesakit CAPD adalah lebih tinggi (0.79 hingga 0.93) berbanding pesakit hemodialisis (0.79 hingga 0.89) bagi tahap kesihatan sempurna yang setara. Kos bagi pesakit hemodialisis setahun adalah RM33,958 manakala bagi pesakit CAPD adalah RM33,243. Kos per QALY bagi pesakit hemodialisis adalah RM43,000 dan RM41,000 untuk pesakit CAPD. Keuntungan QALY yang berterusan pada tahap permulaan hemoglobin untuk pesakit-pesakit hemodialisis adalah 2.04 dan CAPD adalah 0.27. Kos keuntungan bagi setiap QALY yang berterusan untuk EPO pula adalah RM66,000 bagi hemodialisis dan RM137,000 bagi CAPD pada purata permulaan tahap hemoglobin di antara 8 dan 10 g/dl.

Kesimpulannya, jenis rawatan haemodialsis adalah lebih efektif dari segi kos jika dikaitkan dengan penggunaan ubat EPO pada masa ini berbanding CAPD.

Kekunci: Hemodialisis, CAPD, Eritropoietin, Kekurangan Darah, Keberkesanan Kos, Cara Hidup Berkualiti, TTO, QALY, Kementerian Kesihatan Malaysia.

COST EFFECTIVENESS ANALYSIS OF ERYTHROPOIETIN THERAPY IN THE MINISTRY OF HEALTH DIALYSIS PROGRAMME

ABSTRACT

End-stage renal failure patients are normally anaemic due to failure of renal to produce endogenous erythropoietin (EPO). Erythropoietin is used to treat anaemia in these patients but the drug is expensive. The drug is also used in cancer and thalassemia patients and it makes EPO in high demand and thus increasing the budget for the government. The objectives of this study were to determine the life expectancy, the improvement in haemoglobin levels of anaemic patients associated with EPO therapy, the improvement in quality of life associated with haemoglobin, the utility of the dialysis patients, the additional costs associated with EPO therapy and the cost effectiveness of MOH dialysis program, measured as cost per quality-adjusted life year saved. The instruments used for health-related quality of life questionnaires were EQ-5D and Spitzer's quality of life index, and also the time trade-off method. The costs were valued in terms of year 2004 RM. The National Renal Registry (NRR) database for period 1997 – 2004 formed the basis of patient selection, where data was not available the NRR database was used as the sampling frame to obtain the list of patients for the survey. Erythropoietin therapy improved the mean haemoglobin level of anaemic haemodialysis patients by 9.39 % (8.97 g/dl to 9.81 g/dl) and CAPD patients 8.48 % (8.96 g/dl to 9.72 g/dl) at the range of 8 to 10 g/dl. Mean dose of EPO prescribed at baseline haemoglobin level between 8 to 10 g/dl was 4679 U per week for haemodialysis patients and 4477 U per week for CAPD patients. The mean cost to raise 1 g/dl

haemoglobin per patient per year was RM5274 for haemodialysis patients and RM4887 for CAPD patients at same haemoglobin levels.

Overall life expectancy on dialysis was 10.13 years with superior life expectancy for haemodialysis (11.37 years) compared to CAPD (7.94 years). Age at commencement of dialysis, diabetic status, haemoglobin level, albumin level and dialysis modality were significant predictors of life expectancy. Quality of life of CAPD patients was higher among the dialysis patients (0.79 to 0.93) of perfect health equivalent compared to haemodialysis patients (0.79 to 0.89) of perfect health equivalent. The cost of dialysis was RM33,958 for haemodialysis and RM33,243 for CAPD per patient per year. The cost per quality-adjusted life years was RM43,000 for haemodialysis and RM41,000 for CAPD. The incremental QALYs gained for haemodialysis and CAPD patients at haemoglobin baseline were 2.04 and 0.27, respectively. The incremental cost per QALY gained of EPO was RM66,000 and RM137,000 for haemodialysis and CAPD patients, respectively at the same average baseline haemoglobin level between 8 g/dl and 10 g/dl. In conclusion, haemodialysis is more cost effective modality with the current state of utilisation of EPO therapy.

Keywords: Haemodialysis, Continuous Ambulatory Peritoneal Dialysis, Erythropoietin, Anaemia, Cost-effectiveness, Quality of Life, TTO, Quality-adjusted Life Years, Ministry of Health

CHAPTER 1

INTRODUCTION

1.1 BACKGROUND

End-stage renal disease (ESRD) is a severe kidney disease or chronic kidney failure that has reduced the kidney function to 10 percent or less of normal function, requiring the patient to have either dialysis or a transplant in order to live. There were 11,554 end-stage renal disease patients who were on dialysis in Malaysia by the 31st December 2004 (Lim *et al.*, 2005). About one third of them are in the Ministry of Health programme, and the rest are from the non-governmental organisation (NGO), universities, armed forces and private sectors.

The majority of dialysis patients with ESRD have anaemia, defined as a hematocrit less than 33% or haemoglobin levels less than 11 g/dl by the National Kidney Foundation's Dialysis Outcomes Quality Initiative (NKF-DOQI, 1997). The primary aetiology of Chronic Renal Failure (CRF) related anaemia is insufficient production of the renal hormone erythropoietin (Eschbach, 1989). In addition, other factors that contribute to anaemia in CRF include iron deficiency (Eschbach, 1989), hyperparathyroidism (Potasman *et al.*, 1983), acute and chronic inflammatory conditions (Adamson *et al.*, 1989), shortened red cell survival (Eschbach *et al.*, 1967), hypothyroidism (Eschbach, 1995) and underlying hemoglobinopathies (Eschbach, 1995). Among patients with end stage renal failure (ESRF) on dialysis, anaemia may further be accentuated by such factors like aluminium toxicity (Kaiser *et al.*, 1985), folate deficiency (Hampers *et al.*, 1967), haemolysis related to improper dialysate solution (Said *et al.*, 1977) and blood loss related to haemodialysis (Lindsay *et al.*, 1973).

Effective anaemia management, which may improve both survival and quality of life in dialysis patients with ESRF, includes standard clinical interventions applied flexibility according to each patient's need. Using target values recommended by the NKF-DOQI enables clinicians to adjust every patient's haematopoietic parameters to meet current guidelines (Trenkle, 2001; NKF-DOQI, 2001). However, due to economic constraint, and the limited resources to be utilized, hinder the use of the guidelines.

Economic evaluation is a useful tool in the planning and operation of a health care program in the public sector. It provides information for the objective assessment of the relative value for money for competing health care interventions. Public healthcare program evaluation includes determining program effectiveness (outcome assessment), program efficiency (economic evaluation), accessibility (reach ability of services) and equity (equal provision for equal needs) (Tugwell *et al.*, 1985; Phillips *et al.*, 1994).

Evaluation may influence future spending and decision making to improve the program, increase accountability for the large amount of money spent, provide information and communicate achievements if any. The benefit may be that it forces one to be explicit about the beliefs and values that underlie allocation decisions. It helps activity managers in decision making on future expenditure, is useful to stakeholders, instils confidence in the public and tax payer and is part of the duty of care and professionalism in delivering a service (Akauntan Negara, 2004). There is a large resource commitment already in place and this is bound to increase markedly over the next few years (demand exceeds supply).

A study was conducted to determine the cost that was required by patients on dialysis in 1993 (Lim *et al.*, 1999) but this did not include treatment of patients with EPO and did not include living related donor renal transplant (LRRT). The costs were based on an evaluation of Kuala Lumpur Hospital and this may not be generalisable to the rest of Malaysia. Hooi and her colleague (2003) performed the micro costing in their cost effectiveness study but did not evaluate the quality of life component. Erythropoietin may increase the quality of life (QOL) and life years in dialysis patients; its use will increase the cost of dialysis modalities substantially without increase in cost-effectiveness from point of view of health provider (Sheingold *et al.*, 1991; Leese *et al.*, 1992; Moran *et al*; 1992; Whittington *et al.*, 1993; Piccoli *et al.*, 1995).

This research determined the outcomes of dialysis patients given EPO (Eprex® and Recormon®) in the Ministry of Health dialysis program. Outcomes were assessed by life years saved, and their quality of life.

1.2 PROBLEM STATEMENT

A major cause of anaemia in patients with ESRF is insufficient production of erythropoietin by the kidneys. When untreated, the anaemia is associated with a number of physiologic abnormalities, including decreased tissue oxygen delivery and utilization (Horina *et al.*, 1993; Robertson *et al*; 1990; Braumann *et al.*, 1991; Teehan *et al.*, 1989), increased cardiac output, cardiac enlargement, ventricular hypertrophy, angina, congestive heart failure (Wizemann *et al.*, 1993; Harnett *et al.*, 1995; Wizemann *et al.*, 1992), decreased cognition and mental acuity (Wolcott *et al.*, 1989), altered menstrual cycles (Eschbach and Adamson, 1988b; Ramirez *et al.*, 1994; Schaefer, 1989a), decreased nocturnal penile tumescence (Sobh, 1992), and impaired immune responsiveness (Gafter *et al.*, 1994; Vanholder *et al.*, 1993). Anaemia also plays a role in growth retardation in paediatric patients (Scigalla *et al.*, 1989). These physiologic abnormalities reduce quality of life (Evans, 1990), interfere with rehabilitation of chronic renal failure (CRF) patients and decrease patient survival (Lowrie, 1994).

Erythropoietin has also become widely used in Malaysia despite the high cost of therapy. Many guidelines have been issued for the optimal management of renal anaemia (European Best Practice Guidelines for the management of Anaemia in patients with Chronic Renal Failure, 2004; NKF-DOQI, 2001) and recommended the use of EPO as the therapy. However, the EPO is too expensive and taxing to the government budget. The cost of acquisition for Eprex® per vial for 2000 U and 4000 U was RM75.00 and RM154.66, respectively, prior to 2001. The cost of EPO therapy in dialysis program was about RM10 million a year in 2001 (Lim *et al.*, 2002) and about RM45 million in

2004 (unpublished data). The National Renal Registry reported that in 1998, 46% of haemodialysis patients and 44% of continuous ambulatory peritoneal dialysis (CAPD) patients in the MOH program were on EPO treatment, and the proportion receiving EPO has since been steadily increasing to 51% and 44%, respectively in 1999, 56% and 46%, respectively in 2000 and 60% and 48%, respectively in 2001 (Lim *et al.*, 2002). This amounts to nearly 1400 patients on EPO in the MOH program at a cost in excess of RM10 million a year in 2001. In the private and NGO sectors, the proportion receiving EPO were equally high at 62% and 65% of haemodialysis patients, respectively. For 2004, the proportion receiving EPO has leaped to 73% in haemodialysis and 62% in CAPD patients.

However, in spite of the availability of EPO, recent data has shown that the management of the anaemia of chronic renal failure remains less than optimal. Sixty percent of haemodialysis patients were on EPO with 58% on 2000-4000 units weekly. Only 10% of patients on intravenous EPO had haemoglobin concentration more than 12 g/dl, 35% with haemoglobin concentration between 10 and 12 g/dl (Lim *et al.*, 2002). This suggests that dose of EPO given to the patients was less than optimal due to limited resources. Thus, the optimal management of anaemia among patients on dialysis in this country is still very much constrained by economics.

1.3 LITERATURE REVIEW

Recombinant human erythropoietin, epoetin alfa (Eprex®) and epoetin-beta (Recormon®) are indicated for anaemia. This recombinant human erythropoietin has been referred to by several names, including rHuEPO, EPO, Epoetin-alfa or beta and erythropoietin. Erythropoietin is a biologically engineered protein that stimulates the bone marrow to make new red blood cells. Erythropoietin elevates or maintains the red blood cell level as manifested by hematocrit or haemoglobin determinations. People with chronic renal failure suffer from anaemia because they do not produce sufficient amounts of erythropoietin, which is normally produced in healthy kidneys. Clinical trials of EPO were initiated in 1985 to 1986, and replacement therapy with EPO has since become the most rational therapy for anaemia of CRF (Eschbach *et al.*, 1987; Winearls *et al.*, 1986; Eschbach *et al.*, 1989a). These initial trials have convincingly demonstrated that hematocrit could be maintained at a level above 30% in more than 90% of patients. Subsequent studies have shown that the effective correction of anaemia of CRF improves physical performance or exercise (Canadian Erythropoietin Study Group, 1990; Nissenson, 1989; Robertson *et al.*, 1990; Braumann *et al.*, 1991; Metra *et al.*, 1991), sexual function (Nissenson, 1989; Schaefer *et al.*, 1989a; Schaefer *et al.*, 1989b), brain and cognitive function (Nissenson, 1989; Wolcott *et al.*, 1989), and increase quality of life (Harris *et al.*, 1991; Wolcott *et al.*, 1989; Moreno *et al.*, 2000; Revicki *et al.*, 1995; Nichols, 1992; Delano, 1989; Barany *et al.*, 1990; Evans, 1991). While the correction of anaemia for chronic renal failure patient improves with the use of EPO, adequate iron stores must be maintained by oral or intravenous iron supplements (Macdougall *et al.*, 1990; Pollok *et al.*, 1989).

In view of its cost, however, it is essential to exclude and treat other causes of anaemia before considering using this hormone. The treatment is expensive and long term; therefore it is important to be selective in its use. Macdougall *et al.* (1990) recommended that in balancing the benefits and the risks, however, the common practice is to aim at partial correction. A linear increase in the haemoglobin concentration or packed cell volume leads to an exponential rise in the viscosity of whole blood (Macdougall *et al.*, 1990), which, in turn, is thought to contribute to many of the side effects of treatment with EPO such as hypertension increased peripheral resistance, and thrombotic complications. In addition, this partial correction of the anaemia seems to cause near maximal improvement in well-being, exercise capacity (Feeny *et al.*, 1989) and symptoms of anaemia. However, a further increase in the haemoglobin does not confer any additional benefit (Tsutsui *et al.*, 1989) and would therefore be less cost effective.

The target haemoglobin concentration most commonly used is in the range of 100-120 g/l (Macdougall *et al.*, 1990) as compared to 90 –100 g/l (Harris *et al.*, 1991) and 85 –105 g/l (Stevens *et al.*, 1992), at which the ratio of risk to benefit seems to be minimized, though some flexibility is necessary in treating individual patient. Because the main aim of the treatment with EPO is to reverse the symptoms of anaemia, differing thresholds at which this occurs may influence the appropriate final haemoglobin concentration. Stevens (1992) concluded that low dose subcutaneous EPO restores haemoglobin concentration sufficiently to abolish blood transfusion requirements and reduce morbidity and the target haemoglobin concentration was achieved by three months (47 patients) or six months (6 patients). The rate of rise of the

haemoglobin response for most patients, an increase of 10 g/l/month seems sensible (Macdougall *et al.*, 1990). Exceeding this limit may predispose the patient to an increased risk of side effects, and there are rarely any indications for more rapid correction of anaemia.

Given the current climate for health care, which emphasizes cost containment and medical care effectiveness, it will be important to be cost effective. Resources for the provision of health care are scarce, in that there are not, and never will be enough resources to satisfy human needs completely. Therefore, in choosing to use resources in one health care programme or treat, the community forgoes the opportunity to use the same resources in another competing activity. Hence, the economists' notion of opportunity cost; that is, the cost of using resources in one healthcare programme is the value of the benefits they would have generated in their best alternative use (Drummond, 1987a).

Patients' values are fundamental to decision models, cost-effectiveness analyses, and pharmacoeconomics analyses. Much effort has gone into developing techniques to explicitly capture how patients value different health states and outcomes. The most well known methods for assessing these values (i.e., quantifying patients' utilities) are standard gamble and time trade-off. They are well described and have been used in a wide range population (Sox *et al.*, 1988; Torrance, 1987; Weinstein *et al.*, 1980). Assessing how patients value health states, however, can be extremely difficult. Quantitative utility assessment is generally an unfamiliar exercise for most people, and the requisite tasks, considering unfamiliar outcomes, comparing sets of probabilities, and so on, can be challenging.

There are several valuation techniques that are in use namely standard gamble, time trade-off and rating scale (eg. visual analog scale), which are normally used to quantify participants' value for their current state of health (Woloshin *et al.*, 2001; Nord, 1992). These quantities, values or utilities were represented as a number between 0 and 1, with 0 defined as immediate death and 1 defined as perfect health ("the best health you can imagine"). For simplicity, utilities are referred to values for current health elicited with standard gamble, time trade-off, or visual analog scale. The simplest method of obtaining a health state utility is to use judgment to estimate the utility value or to estimate a range of plausible values (Torrance, 1986). Judgments can be simple estimates made by analyst or by a few physicians (Weinstein, 1981), or they can be formal measurements made on a small non-random convenience sample of physicians or other experts (Torrance, 1972).

When judgmental utility values are used, it is essential to undertake extensive sensitivity analysis to determine the robustness of the conclusions. The judgmental approach has been used extensively by the group at Harvard (Weinstein, 1981). It has the advantage of being quick and inexpensive. Moreover, it may be sufficient, if the sensitivity analysis shows that the conclusions are relatively insensitive to wide changes in the utility values (Torrance, 1986).

Utility for current health is determined by assessing the proportion of remaining life expectancy a person would be willing to trade in exchange for living in perfect health. There is a growing literature studies in which utilities have been measured for a few specific heath states. For examples, Sackett and Torrance (1978) presented utilities for depression, home confinement for tuberculosis,

home confinement for an unnamed contagious disease, hospital dialysis, home dialysis, kidney transplant, mastectomy for breast cancer, and mastectomy for injury. Churchill *et al.* (1984a) reported utilities for hospital dialysis and continuous ambulatory peritoneal dialysis. Utilities for loss of speech due to laryngectomy have been reported by McNeil *et al.* (1981). A group at Princess Margaret Hospital in Toronto has reported for cancer related states (Llewellyn-Thomas *et al.*, 1984a). Utilities for different levels of angina pain have been reported in a study (Read *et al.*, 1984).

There are many studies in which a classification system covering a fairly wide range of health states has been established, and utility values have been measured for the states. One is a study by Bush and his colleagues reported in Kaplan *et al.* (1976), which the measurements were performed using a rating scale technique on the general public in San Diego. The other is a McMaster University study reported in Torrance *et al.* (1982) in which measurements were performed on parents of school age children in Hamilton using both the rating scale and time trade-off measures within a multi-attribute utility theory framework. The last example will be the study by Churchill *et al.* (1987), in which the measurement of quality of life in end stage renal disease patients were measured using both rating scale and time trade-off technique.

Cost utility analysis (CUA) is the widely used economic evaluation method to aid decision-making in allocating health resources. This compares the costs of different procedures with their outcomes measured in 'utility based' units. This unit relates to a person's level of wellbeing. The most commonly used unit is quality adjusted life year (QALY) (Fanshel and Bush, 1970; Patrick *et al.* 1973). Quality adjusted life years are calculated by estimating the total life

years gained from a procedure and weighting each year to reflect the quality of life in that year.

The QALY concept is not without controversy (Robinson, 1993a; Gold *et al.* 1996). It has been accused of discriminating against elderly people, making illegitimate interpersonal comparisons, disregarding equity considerations, and introducing bias into quality of life scores (Carr-Hill, 1989; Loomes and McKenzie, 1989). Healthy-Years Equivalents (HYE), the more general approach to assigning preferences to life time paths, has been suggested as an alternative to QALYs (Mehrez and Gafni, 1989). The HYEs are rarely used in the CUA framework. The likely reason for this is practical difficulties associated with their use. Valuation is required for all potential outcomes paths that might result from the interventions in question (Dolan, 2000; Bryan *et al.* 2002). HYEs are calculated by measuring the utility for each possible health path of changing health states and converting this utility through a second measurement into its HYE. There are two essentials components to the HYE approach. One is the measurement of preferences over complete life paths, rather than over discrete health states. The second is the use of two-staged standard gamble assessment procedure in the measurement process. There is considerable dispute over the second component of the HYE approach (Gold *et al.* 1996) and HYE is rarely use in CUA up to date.

The quality adjusted life years has been proposed as a useful index for those managing the provision of health care because it enables the decision-maker to compare the 'value' of different health care programmes and in a way which, potentially at least, reflects social preferences about the appropriate pattern of provision. The index depends on a combination of a measure of

morbidity and the risk of mortality. With additional strong assumptions, utilities can be aggregated across individuals to provide a group utility function. Quality adjusted life year are designed to aggregate, in a single summary measure, the total health improvement for a group of individuals, capturing improvements from impacts on both quantity of life and quality of life.

A crucial aspect of QALYs is the set of weights that are applied to the health states. For any individual (prospective) patient, count one year of current life with a lower level of health, say q where $q < 1$, as worth 'q' QALY units. Adjust the value of a future year of life to a current value by discounting at rate 'r'. Then given the health profile of an individual over their expected future life span, the current value of their expected remaining QALYs can be calculated (Carr-Hill, 1989; Loomes and McKenzie, 1989; Robinson, 1993a). Interventions, procedures treatments change the expected health profile and life span and hence generate a different QALY. The difference in QALYs with or without intervention is the gain (or loss) in QALYs due to intervention. Interventions, which produce more QALY units, are better. When compared with the costs of each intervention, values of cost per QALY gained can be calculated for each intervention. Those interventions with lowest cost per QALY gained are then chosen in preference to any others.

The QALY approach is indifferent with respect to the source of QALYs (Torrance and Feeny, 1989). For example, the approach assumes that it is equally valuable to extend 10 lives for 1 year in a health state with a quality of 0.50, or to extend 5 lives for I year each at perfect health, or to improve the quality of life from 0.6 to 0.85 for 20 individuals for 1 year, or ignoring discounting, to extend one life in full health for 5 years. If the weights are based

on utilities and one accepts the additional assumptions inherent in utility aggregation (mutual utility independence, constant proportional trade-off, and utilities linear with time) these equivalencies follow. It is thus noted that the QALY approach is based on a number of assumptions (Torrance and Feeny, 1989; Carr-Hill, 1989).

The appeal and the power of the QALY approach come from its ability, at least in theory, to capture, in a single summary measure, QALYs gained, the health improvement created by any proposed or existing program or technology regardless of disease, type of patient, or type of program. This allows for broad comparisons across all types of health care technologies. This ability also has its disadvantage. Within specific programs, it is difficult for physicians and managers to interpret the practical meaning of a conclusion that a particular alternative will outperform its rival by so many QALYs gained. Thus, it is recommended that QALY approach be used in conjunction with other, more disaggregated quality of life measures such as a disease-specific and health-profile measures (Torrance and Feeny, 1989; Guyatt *et al.*, 1986). These measures help to provide detailed results or the various effects of interventions to clinicians and health care managers. The two approaches are complementary.

The use of utilities as weights is particularly appropriate (Drummond, 1987b; Torrance, 1987; Sackett *et al.*, 1978; Lane, 1987; Feeny *et al.*, 1989), and such an approach leads to a variation on cost-effectiveness analysis known as cost-utility analysis. The approach has significant potential for increasing the transparency and rationality of decision–making concerned with the adoption and utilization of health-care technologies.

1.4 RATIONALE OF STUDY

The use of EPO to revert anaemia in chronic renal failure patients, even though it is expensive, has immensely benefited the dialysis patients (Wolcott *et al.*, 1989; Canadian Erythropoietin Study Group, 1990; Barany *et al.*, 1990; Whittington *et al.*, 1993; Revicki *et al.*, 1995). The cost incurred by the Ministry of Health of Malaysia was in excess of RM45 million in year 2004 for the use of EPO in anaemic, dialysis patients. Figures from the Twelfth Report of The Malaysian Dialysis and Transplant Registry 2004 showed that there was an increasing in number of dialysis patients being 4534, 5536, 6690, 7830, 9079, 10342 and 11554 in years, 1998, 1999, 2000, 2001, 2002, 2003 and 2004, respectively.

If the incidence of new cases of ESRF remains constant, it is predicted that the number of patients with ESRF will reach 19500 by the year 2010. With a high percentage of the patients that are funded or subsidized by the Ministry of Health, the increase in new patients will signify extra costs to the government every year. The costs associated with maintenance of centre haemodialysis and continuous ambulatory peritoneal dialysis were RM21,620 and RM30,469, respectively, per patient per year in 1996, based on 1737 patients receiving such treatment (Lim *et al.*, 1999) compared to RM33,642 and RM31,635, respectively, patients with actual EPO usage, per patient per year in 2001.

In most countries, the numbers of patients waiting for a donor kidney are increasing. In Malaysia, kidney transplantation is limited by economic constraint and scarcity of donor grafts. This implies that a large proportion of patients will remain in dialysis for sometime, of which many may develop anaemia. This suggests that costs for treatment of chronic renal failure patients form a

substantial part of the health budget for the Malaysian government. The growth in expenditure on health care and the dominance of public sector funding means that the quest for more cost effective use of limited public sector resources is universal.

The decision is on whether the number or percentage of end stage renal failure patients who are anaemic and getting the EPO should be increased or maintained at the present levels, or decreased. Cost effectiveness of this drug would be compared to other claimants on the resources of the Ministry of Health or even for the Malaysian government. For this purpose, effectiveness is taken to be the effect on life expectancy adjusted with the quality of life. Lim *et al.* (1999) has conducted a cost effective evaluation of the Ministry of Health dialysis programme but did not include EPO cost. In 2003, Hooi and her colleagues performed the micro costing in the cost effectiveness study in the dialysis programme. However, the quality of life outcomes on dialysis patients were not conducted due to some methodological difficulties. This study will complement the previous study to give more impact on the economic evaluation of this programme in Malaysia.

From the empirical data, the haemoglobin and hematocrit levels that can significantly produce quality of life could be predicted. In the previous studies, (Duff *et al.*, 1991; Casati *et al.*, 1987; Eschbach, 1995; Eschbach and Adamson, 1988b; Canadian Erythropoietin Study Group, 1991; US Recombinant Erythropoietin Predialysis Patients Study Group, 1991) the treatment with EPO has caused vascular problems particularly hypertension patients, and those with a tendency to thromboembolism. Partial correction of end stage renal failure - related anaemia using EPO has been shown to improve the health-related

quality of life of chronic dialysis (Canadian Erythropoietin Study Group, 1990; Evans *et al.*, 1990; Laupacis, 1991). This improvement is closely linked to the hematocrit level reached during EPO treatment (Moreno *et al.*, 1996; Evans *et al.*, 1990; Adamson *et al.*, 1989; Whittington *et al.*, 1993). Although there is no agreement about what the target hematocrit should be in these patients, the recommended target hematocrit has increased over time. The most recent recommendation of the NKF-DOQI Clinical Practice Guidelines for the Treatment of Anaemia in Chronic Renal Failure suggested that a range of 33 to 39% for hematocrit and 11 to 12 g/dl for haemoglobin level (NKF-DOQI, 2001). These figures are clearly lower than normal, which raises the question of why the dialysis patients are recommended to remain anaemic. The main reason for keeping hematocrit or haemoglobin levels below is the risk of serious adverse effects (cardiovascular events, hypertension, thrombosis of the vascular access) when hematocrit is normalized.

An additional problem with raising hematocrit to normal levels is the increased cost of treatment because of the need for higher EPO doses and iron requirements (Moreno *et al.*, 2000). If the finding in this study show partial correction of anaemia raises the quality of life of end stage renal failure patients, then, it will be an advantage to the Ministry of Health in terms of the cost.

In a study by Besarab *et al.* (1998), these authors do not recommend the administration of EPO to raise hematocrit to normal levels in haemodialysis patients with clinically evident congestive heart failure or ischemic heart disease because of high cardiovascular mortality in these patients. However, there is evidence that a normal hematocrit has beneficial effects on the well-being of dialysis patients (Wolcott *et al.*, 1989; Moreno *et al.*, 2000). It is therefore,

important to know the trend of hematocrit in the dialysis patients in MOH setting. With this finding, the level of hematocrit or haemoglobin that is more appropriate for MOH setting could be suggested. The co-related dose of EPO to achieve the desired target of levels of hematocrit may then be applied for the end stage renal disease patients in future. The management of the doses of EPO and monitoring of the levels of hematocrit or haemoglobin, and iron parameters will then be the guide to determine the optimal levels required for future practice, and will be extrapolated to all end stage renal failure patients in Ministry of Health programmes, even in the NGOs, Army Forces, and private practices.

The health providers may also make comparisons with the data that is collected in this study with those done previously. For example, in controlled multicentre trials of EPO in over 400 haemodialysis patients in the United States for 3 years have shown that in most participants, hematocrit increases at a rate of 1.0% per week for a 50 U/kg dose administered three times a week to 1.8% per week for 150 U/kg administered three times a week (Eschbach and Adamson, 1988a). The patients would benefit from the outcome and the findings that were gathered from this study.

The importance to correct the anaemia in chronic renal insufficiency is great since it is associated with significant morbidity, cost of therapy, many patients are not seeking early medical care, and lack of understanding that prevention of anaemia is important for long-term cost care of the patients with chronic renal failure. In this study, only those who are on dialysis is focussed, and not the pre-dialysis patients who are anaemic. Actually, there is greater discrepancy between the number of anaemic pre-dialysis patients not receiving or benefiting from EPO and those that are being treated with EPO (Eschbach,

1995; Sheingold *et al.*, 1991). Early, preventive therapy with EPO offers a good chance that rehabilitation can be maintained in patients with chronic renal failure after dialysis is required (Ritz *et al.*, 2000; Eschbach, 1995). By completing this research, it is hoped that more recognition is given in that the anaemia is a risk factor for present and future increased morbidity. Since erythropoietin may rapidly evolve widespread use as primary anaemia therapy in end-stage renal disease, identification of potential-limiting factors at either initiation or midcourse of treatment will guide in patients selection for therapy, aid in converting non responders to responders, and in many instances, point to occult pathology responsible for poor response.

It is hoped that this study will trigger more research questions and perhaps, some areas can be explored to optimize the use of EPO and to better manage the anaemia. For example, since there remains a fear that a normal hematocrit will result in many adverse events such as worsening hypertension, access clotting, seizures and under dialysis, these fears need to be addressed by more controlled studies. Another example will be to determine the causes of treatment resistance to EPO therapy so that the resources used will not be wasted.

This study would estimate the quality-adjusted life years for the haemodialysis and CAPD patients in the MOH dialysis program. The QALYs that are calculated by estimating the total life years gained from a procedure and weighting each year to reflect the quality of life in that year can be compared with outcomes of various programmes. One may argue that there is no such study done in Malaysia. In that case, this study will be the pioneer study of its kind and may it trigger more studies to promote cost effectiveness.

In this cost-effectiveness analysis, the perspective adopted is that of the Ministry of Health of Malaysia. Maximum health benefit is the goal, the program is constrained by limited resources and all persons are valued equally.

1.5 STUDY OBJECTIVES

The objectives of this study were to determine the following:

1. Life expectancy of patients on dialysis in the MOH dialysis programme;
2. Improvement in haemoglobin levels of dialysis patients who are anaemic associated with erythropoietin therapy;
3. Improvement in quality of life associated with haemoglobin;
4. Utility of health related quality of life states;
5. Additional costs associated with erythropoietin therapy in the MOH dialysis programme;
6. Cost effectiveness of MOH dialysis program (haemodialysis and CAPD), measured as cost per quality adjusted life year saved.

This research will try to answer three 'what' questions, being: (i) what is the quality of life of the dialysis patients? (ii) What is the cost to bring up 1 g/dl of haemoglobin in those patients? (iii) What is the cost per quality adjusted life years for those patients?

1.6 HYPOTHESES

There is no hypothesis for this study. The reasoning is being explained by Blaikie. Blaikie (2003) divided research questions into three main types: 'what' questions, 'why' questions and 'how' questions. 'What' questions seek descriptive answers, 'Why' questions seek understanding or explanation and 'How' questions seek appropriate interventions to bring about change. It is commonly held view that research should be directed towards testing hypotheses. While some types of social research involve the use of hypotheses, in a great deal of it hypotheses are either unnecessary or inappropriate. Theoretical hypotheses are relevant in any research that requires 'why' questions to be answered. Such hypotheses are possible answers to 'why' questions. It is difficult to answer a 'why' question without having some ideas about where to look for the answer. On the other hand, hypotheses are normally not required to answer 'what' questions (Blaikie, 2000; Blaikie, 2003). The reason being 'what' questions seek descriptions, they can be answered in a relatively straightforward way by collecting relevant data. It is noted that the theoretical use of hypotheses should not be confused with their statistical use. The latter tends to dominate books on research methods and statistics.

Statistical hypotheses are required when data are drawn from probability samples. They allow the researcher to generalize the results found in a sample to the population from which a sample is drawn. When research is conducted on a population or non-random sample, there is no role for statistical hypotheses (Blaikie, 2000).

A theoretical hypothesis does not have strict statistical rules for its testing. It is necessary to make a judgment, on the basis of the evidence, as to how well the data match the form of the proposition in the hypotheses. Therefore, while such hypotheses may state a relationship between two concepts, which become variables in research, the method for testing theoretical hypotheses should not be confused with that used for statistical hypotheses. Whether or not the research involves the use of probability samples, the testing of theoretical hypotheses will be based on a judgment about the patterns and strengths of associations or influences and not on what the level of statistical significance might be.

1.7 SIGNIFICANCE OF THE STUDY

The knowledge and awareness of benefits of EPO in the end stage renal failure will guide towards a better management of renal anaemia. That includes monitoring of iron state, dose of EPO, and route of administration, target haemoglobin concentration or hematocrit level, adverse effects, and the selection of patients that should receive EPO. The potential effects of EPO on medical care expenditures may effect utilization of services through improved health status.

Some medical care utilization that is associated with dialysis patients may be reduced, offsetting some of the costs of this therapy (Shiengold *et al.*, 1992). For example, the reduction or elimination of transfusions for dialysis patients will reduce costs currently incurred for treating anaemia (Shiengold *et al.*, 1992; Eschbach and Adamson, 1988b; Duff *et al.*, 1991). Red blood cell transfusions involve the use of several health care resources including materials, laboratory tests and personnel. In addition on these direct costs, transfusion have been associated with a variety of adverse effects including minor reactions which require some health care resources and serious illnesses such as viral hepatitis and AIDS which are catastrophic when they occur. Thus reduced transfusion requirements associated with EPO will result in less medical expenditure attributable to these illnesses. Another consequence of transfusions for some end stage renal failure patients is allosensitization that reduces the chance of being successfully transplanted. EPO may also affect the extensive pattern of hospitalisation found for dialysis patients, like angina, myocardial infarction (Wizemann *et al.*, 1992; Schwartz *et al.*, 1991), seizure, access clotting and hypertension (NKF-DOQI, 1997). In addition, other

hospitalisation due directly or indirectly to the health status effects of anaemia may decline (Moreno *et al.,* 2000; Harris *et al.,* 1991). On the other hand, hospitalisation due to hypertension and access clotting may increase. Therefore, a consensus on the most cost effective practice may be derived from the experience in this study.

The optimal dosage of EPO and how much dose needed to maintain or improve the patients' quality of life would be known with the results of this study. The experience from this research may help to maintain and improve the quality of life of the end stage renal disease patients. Optimising the use of EPO is beneficial and cost effective in maintaining the quality of life of those patients (Eschbach, 1995). One way is to diagnose and treat the non-EPO-dependent anaemia. While the anaemia of chronic renal failure is primarily EPO-deficient anaemia, there may be other factors that also contribute to anaemia in the patients with chronic renal failure. Correction of this anaemia may result in an increased hematocrit and make it unnecessary to use EPO.

Some patients will have significant erythropoiesis with 25 U/kg subcutaneous or intravenous three times a week, whereas some patients with chronic renal failure may require as much as 150 U/kg at the same frequency (Eschbach *et al.*, 1989a). In addition, most patients would maintain a stable hematocrit of 32 with 20-50 U/kg or less, thrice weekly, assuming the iron states are adequate. The route of administration, which is efficacious for the treatment modality where subcutaneous, is probably the better one, but for some patients the intravenous route is just as effective and may be preferable (Macdougall, 1995). The frequency of administration depends upon the route of administration. Because of its pharmacokinetics, intravenous EPO must be

given at least every 2-3 days. Subcutaneous administration, because of its more prolonged release into the circulation, can result in less frequent administration, such as weekly or occasionally every other week. The administration of EPO should not be discontinued in the chronic treatment of EPO-deficient anaemia except when the unexpected complication of hypertensive encephalopathy occurs. Erythropoietin therapy results in the suppression of endogenous erythropoietin production. In addition, iron stores must also be maintained in order to optimize EPO therapy. Iron is needed for erythropoiesis, but the erythroid demand for iron increases with EPO therapy because it is given in pharmacological boluses. Another way to optimize EPO therapy is by regular monitoring of the haemoglobin or hematocrit, and iron parameters. The iron parameters should be determined prior to the initiation of EPO therapy and monthly during the induction phase of EPO therapy, and then at 2-3 month intervals once maintenance therapy is established.

Having known the cost of increasing 1 g/dl of haemoglobin, the estimate could be done on how much doses would be needed for the patients, and thus the forecasted cost required for future budgeting. Results regarding cost effectiveness of EPO could be compared with those studies done earlier (Moran *et al.*, 1992; Harris *et al.*, 1991; Stevens *et al.*, 1992) where the cost-effectiveness or EPO were calculated as approximately $US2500, $A664, and £290, respectively, to increase hematocrit levels by 0.01%. From these studies, and the limitations described earlier, we can predict whether our practice is comparably cost-effective with the rest.

Clinical guidelines, aided by increasing empirical evidence on the impact of different interventions, are becoming a common manifestation of defining