ANEMIA MANAGEMENT PROTOCOLS IN THE CARE OF HEMODIALYSIS PATIENTS· EXAMINING PATIENT OUTCOMES

by

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ABSTRACT

The role of hemodialysis nurses in renal anemia management has evolved through the implementation of nurse-driven protocols Using the Nursing Role Effectiveness Model, this case control study examined a nurse-driven renal anemia management protocol approach in contrast to a physician-driven approach to assess patient outcomes and costs of renal anemia management from two comparable hemodialysis centres Both protocol and control groups achieved target hemoglobin levels between 110-120 g/L In the protocol group, 75% of patients reached TSAT >20% versus 25% in the control group Iron costs were $17,000 higher in the control group over the study period The protocol group used more epoetin alfa, trending upwards to approximately 10,000 units per person by the end of the study with over $8 000 per person higher costs compared to the control group Evaluation of standardized dosing in renal anemia treatment is suggested for patients with diabetes or cardiac co-morbidities

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

GLOSSARY

Algorithm	A set of clinical steps diagramming a decision tree which directs patient care
BCPRA	British Columbia Provincial Renal Agency, plans and monitors the delivery of renal care in British Columbia
CKD	Chronic kidney disease
EPO	Erythropoietin, amino acid hematopoietic growth factor
ESA	Erythropoietic stimulating agents
ESRD	End stage renal disease
Hgb	Hemoglobin, the oxygen carrying protein molecule in red blood cells
KDOQI	Kidney Disease Outcomes Quality Initiative, recognized as the international standard for evidenced-based clinical practice guidelines for all stages of chronic kidney disease, developed by multidisciplinary nephrology experts
KRP	Kelowna Renal Program serves the Okanagan Health Services Delivery Area with hemodialysis sites in Kelowna, Rutland and Vernon, British Columbia
NH	Northern Health
NREM	Nursing Role Effectiveness Model, A structure-process-outcome nursing model of care developed to examine the contribution that nursing roles have on patient outcomes (Irvine, Sidani & McGillis Hall, 1998)

- The process component identifies three roles of the nurse and categorizes these roles based on the functions or activities of the nurse, independent, dependent, and interdependent roles

- The structure component of the NREM consists of patients, nurses, and organizational variables that impact processes and outcomes of care
- The outcome component of the NREM is the patients' health status, and the direct and indirect costs associated with nursing care
- Nurse-sensitive outcomes are patient outcomes that can be attributed to nursing practice/actions

NRP	Northern Renal Program serves Northern British Columbia, has hemodialysis sites located in Prince George, Terrace and Ft St John, British Columbia
Nurse-driven	That which is initiated and directed by nursing practice
OHDSA	Okanagan Health Delivery Service Area
Physician-driven	That which is initiated and directed by physician practice
PROMIS	Patient Records, Outcomes and Management Information System, database system adopted by British Columbia Provincial Renal Agency
Protocol	Algorithm using evidence-based clinical practice guidelines
RAMP	Renal Anemia Management Protocol based on BCPRA standards and used by the Northern Renal Program
TSAT	transferrin saturation, an indicator of iron status percentage of iron saturating iron binding sites on transferrin

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CHAPTER 1

Introduction

Nephrology nurses in the hemodialysis setting are facing new challenges in the health care system Greater incidence of chronic kidney disease worldwide, coupled with limited financial and human resources in the health care system, have placed significant demands on the hemodialysis nurse In response to these demands, hemodialysis nurses are adopting new approaches to practice to provide safe, economical and effective care Current trends in the hemodialysis setting are placing greater emphasis on enhancing the decision-making role of the nurse to provide clinically sound practice and cost effective care in renal anemia management Increasingly, protocols based on best practice guidelines are followed in the care of the hemodialysis patient The clinical effectiveness of these protocols is commonly measured by patient physiological outcomes such as achieving target hemoglobin levels, transferrin saturation levels and ferritin levels The cost of protocol care can be examined by reviewing the average use of treatments such as erythropoeitin stimulating agents and intravenous iron There is little evidence to show whether using or not using a protocol affects patient and cost outcomes, or whether these differences in outcomes can be attributed to nursing care Using the concepts of structure, process, and outcomes discussed in the Nursing Role Effectiveness Model, this study evaluated two approaches to renal anemia management Outcomes and costs associated with anemia management for hemodialysis patients were examined in two comparable regions within British Columbia (BC) in this case control study

Background and Need

Incidence and Prevalence of Chronic Kidney Disease

Chronic kidney disease (CKD) is defined as the presence of kidney damage for greater than three months with a glomerular filtration rate (GFR) of less than 60 ml/min/1 73 m2, with or without evidence of abnormalities in urinalysis, diagnostic imaging or renal biopsy (Eknoyan & Levin, 2002, National Institutes of Health, 2008) Table 1 classifies CKD into five stages based on GFR level (National Kidney Foundation, 2002)

Table 1
Stages of Chronic Kidney Disease

Stage	Description	GFR (ml/min/m²)
1	Slight kidney damage with normal or increased filtration	≥90
2	Kidney damage with mild decrease in kidney function	60-89
3	Moderate decrease in kidney function	30-59
4	Severe decrease in kidney function	15-29
5	Kidney failure requiring transplantation or dialysis End Stage Renal Disease (ESRD)	<15

Note Adapted from, "National Kidney Foundation (2002) Clinical Practice Guidelines for Chronic Kidney Disease Evaluation, Classification and Stratification," *American Journal of Kidney Diseases,* 39 (Suppl 1) p S1-S266

CKD has a significant impact on society and the health care system Chronic kidney disease is estimated to affect between 1 9 and 2 3 million Canadians (Levin et al , 2008) While there are no statistics available regarding prevalence of CKD in separate regions of British Columbia, the overall estimated prevalence of chronic kidney disease is 145,000 cases (BCPRA, 2008) Patients with CKD have a risk of cardiovascular disease that is ten to thirty times higher than those without CKD (Sarnak et al , 2003) CKD is often associated with anemia, cardiac disease, hypertension, and diabetes all of which require aggressive

chronic disease management CKD is correlated with increased length of hospital stay thereby having an impact on patients, families, society, and health services (Mix et al , 2003)

Stage five CKD is also known as end stage renal disease (ESRD) At stage five, renal replacement therapy (RRT) is required to extend life (Levin et al , 2008) RRT consists of either dialysis or transplantation Hemodialysis and peritoneal dialysis are two forms of dialysis treatment In 2006, 82 1% of all new ESRD patients were started on hemodialysis treatment (Canadian Institute for Health Information, 2008)

Etiology of Chronic Kidney Disease

The etiology of CKD has changed over the past decade Table 2 lists the primary causes of ESRD between 1997 and 2006

Table 2
Percent Distribution of Incident ESRD Patients in Canada by Primary Cause of Renal Failure 1997-2006

Diagnosis	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006
Diabetes	28 9	29 9	31 4	32 1	33 8	33 8	34 2	34 3	35 0	34 4
Vascular	17 8	19 5	20 5	20 3	19 2	18 4	18 6	18 4	19 5	19 5
PCKD	4 7	4 3	4 5	4 7	3 9	4 0	4 2	4 3	5 1	8
GN	5 5	16 0	15 3	13 7	13 3	12 7	12 9	13 1	11 4	11 6
Pyelonephritis	4 7	4 7	4 5	4 0	4 1	4 2	4 3	4 5	3 9	3 5
Drug induced	1 6	1 7	1 3	1 8	2 1	2 1	2 0	1 8	2 0	1 7
Unknown	15 8	13 1	12 5	11 8	14 0	14 7	14 3	13 5	12 2	12 9
Other	10 9	10 8	9 9	11 5	9 7	10 1	9 5	10 1	10 9	11 7

Adapted from Canadian Institute for Health Information, *2008 Annual Report—Treatment of End-Stage Organ Failure in Canada, 1997 to 2006* (Ottawa, Ont CIHI, 2008) ISBN 978-1-55465-391-1 (PDF) Note PCKD- Polycystic Kidney Disease, GN- Glomerulonephritis

Diabetes has remained the most prevalent cause of ESRD in Canada Diabetic nephropathy was the leading cause of renal failure between 1997 and 2006 in Canada, with incidence rates increasing to 34 4% of all new cases of renal failure in 2006 (Canadian Institute for Health Information, 2008) The global increase in the incidence and prevalence

of diabetes over the last twenty years has had a direct impact on the incidence of CKD and the need for dialysis treatment

The second most common cause of ESRD is hypertensive/vascular disease In the United States between 1990 and 2001, the incidence of ESRD related to hypertension has increased by almost 50% (Eustace & Coresh, 2005) Since 1997, the incident rates of ESRD related to vascular disease have increased minimally in Canada from 17 8 % to 19 5 % These differences may be related to better treatments of hypertension in the last decade, therefore reducing the rate of renal disease related to vascular disease Hypertension is both a cause and consequence of ESRD Over 75% of CKD patients develop hypertension related to an inability of the kidney to regulate blood pressure (Levin et al , 2008)

Other causes of CKD are glomerulonephritis (GN), polycystic kidney disease (PCKD) and obstructive uropathy (Pereira, Sayegh & Blake, 2005) Glomerulonephritis is the third leading cause of ESRD in Canada Within the last decade, there have been decreasing trends in the incidence of glomerulonephritis and pyelonephritis and nearly unchanged rates of PCKD in Canada (Canadian Institute for Health Information, 2008)

Hemodialysis Treatment for ESRD

Hemodialysis is derived from two terms, hemo meaning "blood" and dialysis meaning "to pass through" Blood is passed through a semi-permeable membrane by diffusion to separate toxic wastes, excess water and electrolytes from the blood (American Nephrology Nurses' Association, 2007b) The overall treatment goal of hemodialysis is to correct electrolyte and fluid imbalance in addition to removing uremic toxins (Levin et al , 2008), completed by the continuous flow of blood across a dialyzer membrane (Yeun & Depner, 2005) A concurrent passage of dialysate solution along the opposite side of the semi-permeable membrane provides an environment in which loss of solutes can occur via

diffusion (Nesrallah, Blake, & Mendelssohn, 2005) If these goals of dialysis are met, the patient may have improved survival by reducing the effects of uremia and its complications

Hemodialysis is the most common form of renal replacement therapy available to those patients with stage five CKD (American Nephrology Nurses' Association, 2007b) Conventional hemodialysis consists of 3 to 4-hour treatments, three times a week (Levin et al , 2008) In Canada, 47 7% of all hemodialysis patients are provided treatment in a hospital setting (Canadian Institute of Health Information, 2008) In 2005, 57 3 % of hemodialysis patients in B C received treatment in a hospital, while 36% received treatment in a community dialysis unit, with the remainder being dialyzed at home (Canadian Institute for Health Information)

Nationally, the demand for renal services, in particular RRT, is increasing each year There were estimated 33,832 ESRD patients in Canada in 2006, which corresponds to an increase of 69 7% since 1997 (Canadian Institute for Health Information, 2008) In Canada, the incidence of ESRD and those requiring RRT among patients 75 years and older has more than doubled from 1996 to 2005 (Canadian Institute for Health Information) In British Columbia, the increase in the number of hemodialysis patients is considerable In 1996, there were 747 hemodialysis patients, while in 2005 there were 1812 hemodialysis patients (Canadian Institute for Health Information) These trends indicate the growing need for RRT in addition to the provision of efficient and fiscally responsible resource allocation of renal services within the health care system

The outcome of patients on dialysis remains poor The one year survival rate of hemodialysis patients in Canada for 2004 was 81 7% (Canadian Institute for Health Information, 2008) In 2008, the one year survival rate of hemodialysis patients in British Columbia was 83% (British Columbia Provincial Renal Agency, 2008) The three year

survival rate for hemodialysis patients in Canada was 57 7% in 2003 (Canadian Institute for Health Information) Between 1996 and 2005, the five year survival rate for Canadian patients on dialysis was approximately 40% (Canadian Institute for Health Information)

The overall five year survival rate of hemodialysis patients in Canada shows differences in ethnicity Patients of Black and Asian origin showed an unadjusted five year survival rate of 61 7% and 55 6% respectively Patients of Aboriginal and Caucasian origin had the lowest survival rates of 42 5% and 36 3% respectively (Canadian Institute for Health Information, 2008) Prevalence of ESRD among Aboriginals in Canada is 58 4% higher than in non-aboriginals (Canadian Institute for Health Information)

Regional Settings

This study compared two British Columbia regional hemodialysis programs consisting of the Northern Renal Program (NRP) and the Kelowna Renal Program (KRP) The NRP services all renal patients located within the Northern Health (NH) The KRP serves all patients within the Okanagan Health Service Delivery Area (OHSDA)

This section will provide a comparison of demographics in a health region (NH) and a sub region of Interior Health (IH) identified as the OHSDA NH provides health care to 7 5% of the population of British Columbia (BC) encompassing a geographical area of 66 7% of BC (BC Stats, 2007a) The KRP provides renal care to the OHSDA, which serves over 3 5% of BC's population covering 3 3% of the area of BC (BC Stats, 2007b) A comparison of age, ethnicity, family income and aboriginal descent between the two health jurisdictions indicate some differences for these variables between these communities

The Northern Health (NH) has a younger population than the Okanagan Health Service Delivery Area (OHSDA) in all age categories (Figure 1) The OHSDA has an aging population with 19 7 % above the age of 65 years compared to 9 6% in NH region (BC Stats,

2007 a,b) NH has a higher South Asian and Filipino population in comparison to the OHSDA (Figure 2) At 15 6% (BC Stats), NH also has the highest rate of aboriginal persons living in the region compared to the OHSDA and all other BC health authorities (Figure 3) The OHSDA has 69 2% of its population falling within the $20,000-$79,999 income bracket in contrast to NH at 58% (BC Stats) In the NH region, 29 1% of its population has a family income bracket over $80,000 which is higher than the OHSDA at 19 9% (Figure 4)

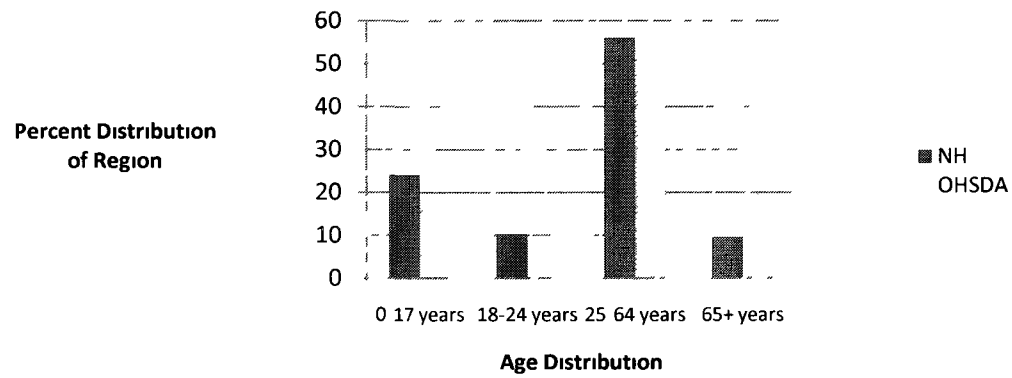

Figure 1 Comparison of age distribution in Northern Health and the Okanagan Health Service Delivery Area (BC Stats, 2007a)

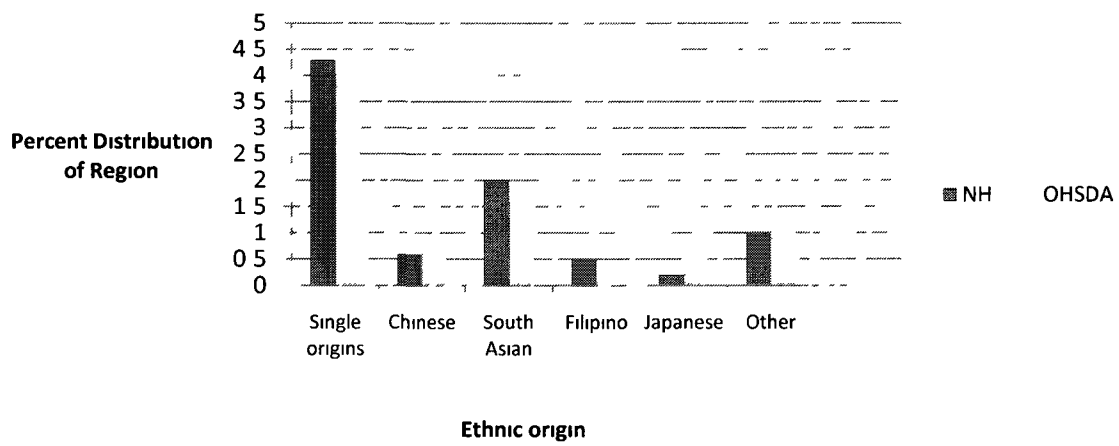

Figure 2 Comparison of population ethnic origins Northern Health and the Okanagan Health Service Delivery Area (BC Stats, 2007a) Note Single origins-indicates a single ethnic origin other than ethnicity displayed on figure, e g Canadian, English, French, First Nations, other European

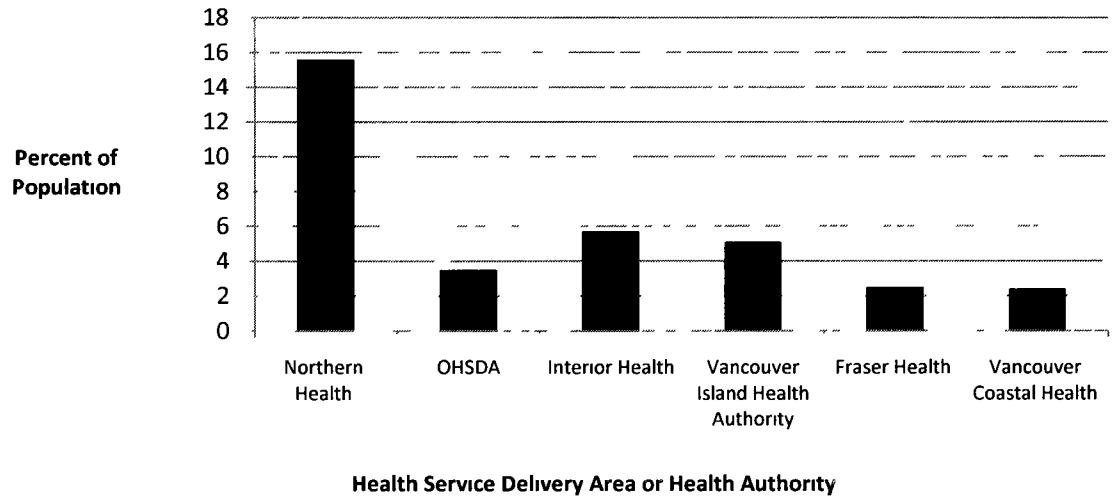

Figure 3 A comparison of the aboriginal populations in BC (BC Stats, 2007a)

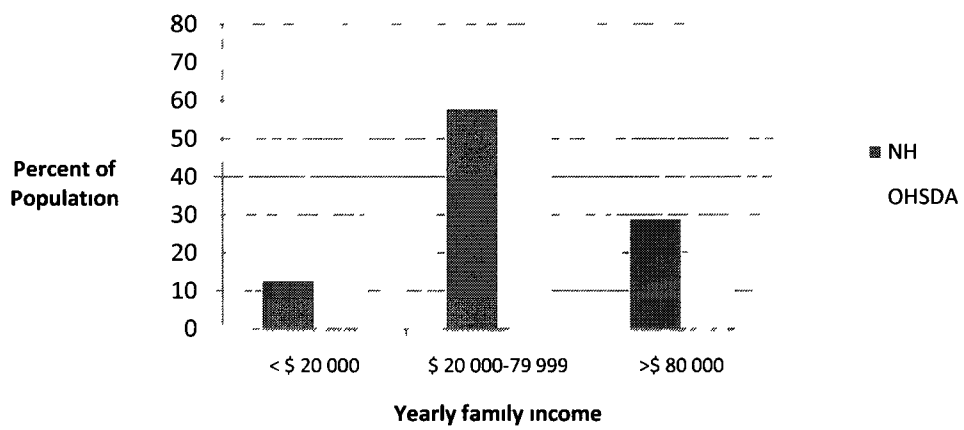

Figure 4 A comparison of the income distribution between Northern Health and the Okanagan Health Service Delivery Area (BC Stats, 2007a)

The differences between the region (NH) and the subregion (OHSDA) may have affected the outcomes of this study As the OHSDA has an aging population, the rates of hemodialysis patients within this age range were higher than NH The higher rates of Aboriginal persons in NH corresponded to higher rates of hemodialysis patients within the

NRP When examining the income distribution of both regions, no conclusions were drawn as to the effect on the hemodialysis population in this study

Current Trends in the Management of Renal Anemia in ESRD

Significance of Study

Nephrology is a specialty in which health professionals work together in a system of interdependent roles to provide patient care At times, these roles will change based on organizational change or changes in the protocols or the structure of decision-making that directly meets patient needs (Sidani & Braden, 1998) Change in nursing practice has always been a part of the nephrology nursing As early as the 1960's, as technology in nephrology progressed, nephrology nurses embraced more responsibilities and autonomy with dialysis treatments (Fulton & Cameron, 1989) Often these changes were due to limited financial and human resources in the health care system Based on the current trend of increasing prevalence of ESRD, a shortage of nephrologists is evident in the health care system (American Nephrology Nurses Association, 2007a) Nephrology nurses are increasingly working to full scope of practice as clinical decision support tools are utilized

Successful management of anemia through implementation of clinical practice guidelines can greatly improve patient outcomes (National Kidney Foundation, 2007) Although clinical practice guidelines may have been used prior to the anemia protocol implementation, the patient outcomes could not be attributed to a nurse sensitive intervention since the care was physician-driven and dependent For this study, Sidani's (1998) Nursing Role Effectiveness Model (NREM) was used as the framework to delineate the relationship between structure, process and outcomes in a specific nephrology nursing context This model frames the context of the nurse changing from a dependent role to an independent role in renal anemia management

Outcomes are an essential aspect of evaluating the contributions of a profession Many researchers describe a link between outcomes and interventions in the health care system (Donabedian, 1985, Doran, 2003, Newell, 1996, Sidani & Braden, 1998) It can be challenging to identify appropriate outcomes that result primarily from nursing care, but this is a necessary aspect of professional accountability and high quality patient care (Doran, 2003, Frauman & Gilman, 2001) Nurse sensitive outcomes are those outcomes which can be directly affected or influenced by nursing care (Frauman & Gilman, 2001) With financial restraints and limited nursing resources, it is imperative that nurses show that the care resulting from their actions leads to positive patient outcomes

Evaluation of nephrology nursing interventions is commonly measured by physiological patient outcomes Patient outcomes such as the adequacy of dialysis, blood pressure, fluid status, pulse and respiratory rate are based on nurses' assessment and intervention before and during a hemodialysis run (Burrows-Hudson & Prowant, 2005, Frauman & Gilman, 2001) A measureable patient outcome for anemia management as an aspect of nephrology nursing care is achieved by maintaining target hemoglobin (Hgb) levels (Burrows-Hudson & Prowant, 2005) Appropriate assessment, decision-making and nursing interventions in anemia management produce physiological patient outcomes that can be considered nurse sensitive

Hemoglobin is the best indicator anemia management Nurses can keep Hgb levels stable through the use of an algorithm Consequently, Hgb levels can be seen as a nurse sensitive outcome It is essential that nurse sensitive measures demonstrate how nursing actions influence patient outcomes

The goal of renal anemia management is to provide Hgb levels within an acceptable target range Evidence shows that effective renal anemia management takes into

consideration the interdependent relationship between iron status, intravenous iron use, erythropoietic stimulating agent (ESA) use and Hgb These factors, properly managed are associated with reduced mortality and hospitalization among hemodialysis patients (Easom, 2006, Elliott, Pham, & Macdougall, 2008, Pisoni et al , 2004) Appropriate renal anemia management requires evaluation of iron status and ESA dosing to improve patient outcomes

The use of decision support tools, such as algorithms, can assist nurses to care for the complex patient A decision-making tool is an evidence-based document used by nurses to guide the assessment, diagnosis and treatment of specific client clinical issues (College of Registered Nurses of British Columbia, 2008) These tools can support nurses as they assume increasingly independent practice in chronic disease management and reduce variation in client care related to individual practitioner practices (Dickerson, Sackett, Jones, & Brewer, 2001) The goal of using decision support tools is the achievement of positive patient outcomes in an efficient, cost effective and continuous manner

Algorithms can be based on guidelines as outlined by the specialty and provide guidance in decision-making They are not a replacement for clinical judgment Algorithms or protocols can present evidence-based guidelines in visual form and enable nurses to outline aspects of disease management in order to make decisions about assessment, treatment and evaluation of care (Dickerson et al , 2001)

Since 2006, algorithms in anemia management for hemodialysis patients have been mandated as standard practice in British Columbia (BC) by the British Columbia Provincial Renal Agency (BCPRA) The BC Medical Advisory Committee recommends that all BC Health Authority Renal Programs use algorithms for efficient use of erythropoietic stimulating agents and of nephrologists' time (British Columbia Provincial Renal Agency, 2007) Each health authority in British Columbia has the autonomy to develop an anemia

management protocol using the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines (British Columbia Provincial Renal Agency) The anemia management algorithm used in the NRP is based on evidence for managing renal anemia as outlined in the (KDOQI) practice guidelines (National Kidney Foundation, 2006)

At the time of the study, the KRP used the KDOQI guidelines for renal anemia management based upon a traditional physician-driven approach A traditional physician-driven approach consisted of monthly rounds with a review of patient blood work A charge nurse was present at rounds to provide blood work results and discuss each patient Adjustment of erythropoietin and intravenous iron doses was completed during rounds Any critical lab values were addressed urgently as necessary Table 3 outlines the differences between a physician-driven approach to anemia management and a nurse-driven protocol approach

Table 3
Differences of Anemia Management Practice in Physician-driven and Nurse-driven Protocol Approaches

Anemia management practice	Physician-driven approach	Nurse-driven protocol approach
Responsible for assessment, monitoring and evaluation of anemia blood work (Hgb, TSAT, Ferritin levels)	Nephrologist	Hemodialysis nurses
Procedure for adjustment of erythropoietin stimulating agents and intravenous iron doses	Nephrologist adjusts medications during monthly rounds and urgently as needed	Hemodialysis nurses adjust medications using step-wise instructions outlined in RAMP when lab work results are available
Evaluation of effectiveness of treatments	Nephrologist evaluates treatment during monthly rounds	Hemodialysis nurses provide ongoing evaluation of treatments using instructions in RAMP

Within the NRP, the introduction of a renal anemia management protocol (RAMP) (Appendix A) resulted in a change in the role of the registered nurse in the care of the hemodialysis patient This change encompassed greater assessment, monitoring and decision-making within the scope of the registered nurse Anemia management has traditionally been the physician's role with minimal nurse input or action

The RAMP transfers anemia management of hemodialysis patients to nurses upon order of the nephrologist Based on general RAMP guidelines, all patients have monthly lab work drawn to assess Hgb status Depending on Hgb status, the protocol provides step-wise instructions on how to titrate an ESA or provide iron therapy Steps for monitoring Hgb status are also provided in the protocol The targeted Hgb for this adult protocol is between 110-125 g/l Transferrin saturation level is targeted between 20% and 50% The ferritin levels are recommended between 200-500 ug/L These targets were agreed upon by the RAMP committee based on the KDOQI guidelines at the time of printing This protocol enables the nephrology nurse to treat anemia in a timely manner

Research Context

This study compared patient outcomes in two settings Patients from the KRP served as a control group using data between November 2005 and November 2006 when an anemia protocol was not in use The NRP was identified as the protocol group during a time period that the protocol was in use from October 2007 to October 2008 The difference in time periods is due to the introduction of an anemia protocol in one of the community units linked to the KRP after December 2006 The KRP is considered to be a control population based on its comparable size in numbers of patients and the inclusion of two community units located in Vernon and Rutland, BC The KRP also has an organizational structure similar to the

NRP based on the British Columbia Provincial Renal Agency (BCPRA) renal program guidelines (British Columbia Provincial Renal Agency, 2004)

The NRP provides renal services for all residents of Northern Health in BC This area encompasses the Northwest, Northern Interior and Northeast health service delivery areas in the province The primary renal management centre is located at the University Hospital of Northern British Columbia (UHNBC) in Prince George, BC Hemodialysis services consist of an in-centre hemodialysis unit at UHNBC and interdependent community dialysis units located at Terrace and Fort St John The UHNBC hemodialysis unit serves as the regional base for both community units In October 2007, there were 73 in-centre hemodialysis patients, 17 Fort St John community patients, and 14 Terrace community patients in the program (British Columbia Provincial Agency, 2008) for a total of 104 patients with approximately 60 patients on the RAMP

The KRP provided renal services to all hemodialysis patients in the OHSDA The primary regional unit is in Kelowna General Hospital and two interdependent community units are located in Rutland and Vernon, BC In October 2005, there were approximately 38 Kelowna in-centre patients, 19 patients in the Rutland unit and 25 patients in the Vernon unit At this geographic location, 82 patients were not on an anemia protocol

Through a retrospective, non-equivalent, group design, this study looked at the impact of implementing a decision support tool within the NRP hemodialysis population The outcome variables evaluated included Hgb levels, transferrin saturation levels, ferritin levels in addition to intravenous iron and ESA use An exploration of the relationship between interventions and outcomes in two comparable hemodialysis populations occurred

Research Questions

The introduction of the RAMP in the NRP arose from the need to better manage Hgb levels for patients with renal anemia The trend of exceeding Hgb targets was of concern for patient safety and cost effective use of ESA's The goal of this study was to provide evidence concerning whether the use of a nurse-driven decision making tool in the hemodialysis setting could result in effective and safe patient outcomes compared to traditional physician-driven approaches to anemia management There are two research questions that were explored in this study

1) In the hemodialysis population, does using a nurse-driven anemia management protocol enable patients to maintain target Hgb levels as effectively as a non-protocol based physician-driven approach?

2) Is there a relationship between anemia management practice approach and Hgb levels, iron levels, intravenous iron use and erythropoietin use in the hemodialysis setting?

CHAPTER 2

Review of Literature

The treatment of renal anemia requires an understanding of the impact ESAs and intravenous iron have on patient outcomes such as target Hgb levels and iron levels in the body The use of decision making tools such as algorithms or protocols, directs the nurse with steps to treat, monitor and evaluate renal anemia management Using the evaluation framework of the Nursing Role Effectiveness model (NREM), this study will apply its concepts to nurse-driven renal anemia management

Renal Anemia

Anemia is a condition marked by a reduction of red blood cells in the body (National Institutes of Health, 2008) Although there are many contributors to anemia, renal anemia is unique to end stage renal patients as it directly relates to erythropoietin deficiency in the body Erythropoietin is vital to the development of red blood cells

Erythropoiesis is a physiologic process of maintaining oxygen levels in the body through the actions of erythropoietin (Elliott et al , 2008) The release of erythropoietin directly corresponds to oxygen levels in the body (Elliott et al) Hypoxia, which triggers a renal oxygen sensor in the kidney, leads to an increase in the production of erythropoietin resulting in the development of red blood cells (Hodges, Rainey, Lappin, & Maxwell, 2007, National Institutes of Health, 2008, Tranter, Martinez, & Rayment, 2006) By increasing the concentration of red blood cells and Hgb, the oxygen carrying capacity is improved

Decreased erythropoietin (EPO) production in chronic kidney disease is the primary cause of renal anemia (Dalton & Schmidt, 2008, Drueke et al , 2006, Levin, 2007, Singh, et al , 2006) Renal anemia is a common complication of kidney failure (Collins et al , 2005, National Kidney Foundation, 2007, Singh & Hertello, 2005, Strippoli, Navaneethan, &

Craig, 2006) At Stage 5 CKD (Table 1), also known as ESRD, 60-80% of patients are affected by renal anemia (Hsu, Mcculloch, & Curhan, 2002)

There are various factors which can influence the development of anemia in hemodialysis patients Hemodialysis patients can experience gastrointestinal bleeding, shortened erythrocyte survival time of 30-60% of the normal 120 days, iron deficiency and increased blood losses at hemodialysis runs (O'Mara, 2008, Pisoni et al , 2004) Increased hemolysis related to the toxic effects of uremia can also exacerbate anemia in the hemodialysis patient (Pruett, Johnson, & O'Keefe, 2007)

Anemia in hemodialysis patients has significant consequences Anemia is associated with decreased exercise capacity, reduced cognitive function, depression, and decreased quality of life (Ludwig & Strasser, 2001, Painter et al , 2002, Silverberg et al , 2003) Renal anemia can have a negative impact on cardiac function due to vasodilation, cardiac dilation, increased cardiac output leading to left ventricular hypertrophy, and congestive heart failure (Locatelli et al , 2007, Silverberg, Iaina, Wexler, & Blum, 2001) Between 1996 and 2005, cardiac failure was the leading cause of death among end stage renal disease patients in Canada (Canadian Institute for Health Information, 2008)

Treatment of anemia has the potential to improve the strength and function of muscle as well as improve cognitive and brain electrophysiological function due to an increase in peripheral oxygen supply (Mason & McMahon, 1997, McMahon et al , 2000) Effective anemia management is associated with lower morbidity and mortality among hemodialysis patients (Brattich, 2006, Pisoni et al , 2004)

Erythropoietin and ESA Therapy

Erythropoietin (EPO) is an amino acid hematopoietic growth factor of which approximately 90 % of EPO is produced by the kidneys (Drueke et al , 2006, Elliott et al ,

2008, O'Mara, 2008) If there is damage to the kidney, its ability to produce adequate amounts of erythropoietin is compromised (O'Mara) Renal anemia is treated by supplementing reduced erythropoietin levels in the body with erythropoietic stimulating agents (Cody et al , 2005, Dalton & Schmidt, 2008)

EPO acts on the bone marrow to stimulate red blood cell production The bone marrow manufactures red blood cells through a series of events The stem cell also known as the hematopoietic progenitors differentiate into burst-forming erythroid cells and then colony-forming erythroid cells Each colony-forming erythroid cell has erythropoietin receptors and is erythropoietin dependent EPO is required to attach to the erythropoeitin receptor on the erythroid cell to continue process of producing red blood cells The erythroid cell is then differentiated into erythroblasts, reticulocytes and mature erythrocytes respectively (Elliott et al , 2008)

The magnitude of increase in red blood cell concentration is controlled by the length of time EPO concentrations are maintained and not by the EPO level itself (Elliott et al , 2008) As a result, measuring EPO levels has little significance in renal anemia management The aim of renal anemia management is maintaining consistent EPO concentrations over time to impact Hgb levels

The maintenance of adequate EPO levels is affected by several factors The balance between red blood cell production and destruction can be influenced by blood losses and kidney defects in oxygen sensing (Elliott, et al , 2008) Particularly in CKD, inadequate concentrations of erythropoietin and reduced life span of the red blood cell trigger an imbalance in erythropoiesis resulting in renal anemia

Erythropoietic stimulating agents (ESA) are genetically engineered forms of the naturally occurring human erythropoietin hormone Epoetin alfa was the first ESA to be

developed and is administered 1 to 3 times per week with dosing based on weight of the patient, 50-100 units/kg (Duh, Weiner, White, Lefebvre, & Greenberg, 2008) Epoetin beta is another form of ESA with similar starting doses as epoetin alfa Darbepoetin alfa is another form of erythropoeitin with a longer half life than epoetin alfa, taking 3 to 5 times longer to reach peak serum concentrations (Duh et al) Starting doses for Darbepoetin alfa are 0 45 μg/kg at weekly to every three week intervals (Duh et al)

Erythropoietic stimulating agent (ESA) therapy, also known as erythropoietic hormone replacement therapy (EHRT), has become the first line of treatment for more than 90% of hemodialysis patients (National Institutes of Health, 2008, Patel, Robinson, & Singh, 2007) ESAs have changed the way renal anemia is treated and this treatment is associated with decreased mortality, morbidity, disease progression, cardiovascular risk, and an improvement in quality of life in hemodialysis patients (O'Riordan & Foley, 2000, Ritz & Eisenhardt, 2000)

Prior to the use of ESAs, blood transfusions exposed the hemodialysis population to considerable risk Repeated blood transfusions do little to maintain Hgb at a target level and can cause iron overload (Bennett, 1998, Easom, 2006) Blood transfusions can also sensitize a patient to develop antibodies in the blood or viral infections, placing them at risk of unsuccessful transplant matches (Bennett) After exposure to Human Leukocyte Antigens (HLA) in previous blood transfusions, a patient can develop antibodies against HLA antigens resulting in difficulty finding a suitable transplant organ and increased risk of rejection of the organ (Magee, 2005) Blood transfusions can also introduce viral infections such as Hepatitis B, Hepatitis C, and Cytomegalovirus to the patient (Magee) Ideally, the use of ESAs can reduce the need for blood transfusions and can contribute to successful future transplantation

Erythropoietic stimulating agent dosing varies with clinical indication, practitioner and geographic region (Elliott et al , 2008) Results from the Dialysis Outcomes Practice Patterns study (DOPPS) of 12 countries demonstrate variable ESA dosing patterns worldwide (Pisoni et al , 2004) These differences are influenced by patient co-morbidities, hospitalization rates, national and regional practice guidelines, in addition to practice patterns (Pisoni et al) These variations account for many of the differences of patient outcomes worldwide

Hyporesponse of hemodialysis patients to ESAs is identified in literature Hyporesponse to epoetin alfa is recognized as a potentially modifiable occurrence correlated to the following factors inadequate epoetin doses, blood loss, acute inflammation or infection, iron deficiency, poor nutritional status, and vitamin deficiency (Deziel, 2002, Kalanatar- Zadeh et al , 2009, National Kidney Foundation, 2006) High bone turnover disease as indicated by elevated serum alkaline phosphatase and parathyroid hormone levels has been correlated with ESA hyporesponse (Kalantar-Zadeh et al)

Hyporesponse to epoetin alfa in hemodialysis patients is correlated with inflammation and malnutrition (Chawla & Krishnan, 2009) Literature shows that elevated pro inflammatory biomarkers such as c reactive protein (CRP) levels are present in some hemodialysis patients and coupled with low albumin levels, can be predictors of epoetin alfa hyporesponse (Breiterman-White, 2006, Deziel, 2002) Studies have demonstrated that high inflammatory biomarkers correlate with incidence of congestive heart failure, coronary heart disease, and vasculitis (van Tellingen et al , 2002) A patient with an inflammatory disorder, as evidenced by high ferritin levels, could require increases in epoetin alfa doses to maintain Hgb levels at acceptable targets (Drueke, 2001) Inflammation in diabetic hemodialysis patients is common as a result of the presence of atherosclerosis, proteinuria, diabetic

neuropathy, diabetic retinopathy, and infections (Jenq, Hsu, Huang, Chen, Lin, & Lin-Tan, 2009)

The use of ESAs in the United States is on the rise and this has a significant impact on the financial resources of renal programs There has been a dramatic rise in epoetin dosing between 1993 and 2005 (National Institutes of Health, 2008) In the United States, between 1991 and 2005, the mean monthly Hgb in dialysis patients rose 24 g/L and the weekly EPO doses rose threefold to over 19,000 units (National Institutes of Health) ESA's account for 10% of ESRD costs of all patients on hemodialysis or peritoneal dialysis (National Institutes of Health)

Iron

The most important goal of iron therapy is to support optimal erythropoiesis to allow target Hgb levels to be reached and maintained It is crucial that careful monitoring of iron status and the dosing of iron therapy take into account the uniqueness of each patient An essential component of anemia management is the routine monitoring of iron status (Easom, 2006) KDOQI guidelines recommend iron status measurement every 3 months during stable ESA treatment (National Kidney Foundation, 2006) Regular monitoring of iron levels is a vital part of anemia management in the hemodialysis patient for several reasons

It is common for hemodialysis patients undergoing ESA treatment to experience "functional iron deficiency" (Pruett et al , 2007, p 207) Iron deficiency is multi-factorial in the hemodialysis patient Iron deficiency can be due to retention of blood in the dialyzer and tubing as well as frequent laboratory tests (Singh & Hertello, 2005) Patients can fail to adequately respond to ESAs due to iron deficiency, as iron is a necessary component to complete the red blood cell production cycle (National Kidney Foundation, 2006) ESA treatment also increases erythropoiesis at rates higher than normal to support Hgb synthesis,

thus increasing the demand for iron faster than can be released from iron stores in the body (Pruett et al) Although the absorption of iron by the body increases as much as five times normal during erythropoietin therapy, losses from hemodialysis and blood testing may exceed gastrointestinal iron absorption (Fishbane, Frei & Maesaka, 1995, Skikne, Ahauwalia, Fergusson, Chonko, & Cook, 1998, Skikne & Cook, 1992)

Transferrin saturation (TSAT) and ferritin levels are often used to diagnose and treat iron deficiency in hemodialysis patients (Singh, Coyne, Shapiro, & Rizkala, 2007) TSAT is a measure of iron stores available for red blood cell production corresponding to the circulating iron bound to transferrin (Kalantar-Zadeh et al , 1998) Greater TSAT has a positive association with effective anemia control (Pisoni et al , 2004) Serum ferritin is the amount of iron stored in the body as released by tissues (Easom, 2006, Kalantar-Zadeh, Rodriguez, & Humphreys, 2004) Ferritin levels alone are "an imprecise marker of iron status due to inflammatory factors which may interfere with synthesis and clearance of ferritin" (Easom, p 545)

ESRD, hemodialysis, infections and protein energy malnutrition are factors which can activate the inflammatory response (Easom, 2006) Serum ferritin levels can increase during inflammatory disorders Inflammation iron block occurs resulting in a type of functional iron deficiency potentially disrupting erythropoiesis (Easom) Inflammation within the hemodialysis population may be as high as 40% to 60% (Kalantar-Zadeh et al , 2004) Elevated serum ferritin (500-2000µg/ml) should not be a marker for excessive iron but could be an "indication of iron plus inflammation in hemodialysis patients" (Easom, p 547) Nephrology nurses must use critical clinical thinking when interpreting KDOQI guidelines of serum ferritin of 500 µg/ml as an upper limit for withholding intravenous (IV) iron therapy

(Easom) Nephrology nurses must evaluate each individual patient's response to IV iron based on ESA responsiveness, Hgb level, and clinical status

Intravenous (IV) iron administration is the preferred route for hemodialysis patients There is a strong recommendation for treatment with intravenous iron within the hemodialysis setting in clinical guidelines (National Kidney Foundation, 2006) In a systematic review and meta-analyses of hemoglobin outcomes in hemodialysis patients using oral iron versus intravenous iron, the better hemoglobin response was with the patients treated with intravenous iron (Rozen-Zvi et al , 2008) Three randomized control trials comparing IV iron with oral iron administration in hemodialysis patients showed that the use of IV iron resulted in greater Hgb levels and reduced the need for higher ESA doses when compared with patients using oral iron (Fishbane, Frei, & Maesaka, 1995, Fudin, Jaichenko, Shostak, Bennett, Gotlob, 1998, Macdougall et al , 1996)

In the past, iron overload was a legitimate concern in the care of hemodialysis patients Blood transfusions were common in hemodialysis patients and resulted in up to 6 g of parenteral iron per year (Easom, 2006) Iron, in the absence of erythropoiesis proved to be detrimental to the patient The greater use of ESAs coupled with the reduced need for blood transfusions has resulted in a reduced risk of iron overload in hemodialysis patients (Easom) It is unlikely that iron overload could occur with the use of appropriate intravenous iron dosing

There are three forms of intravenous iron used in the RAMP (Appendix A) Iron dextran, iron sucrose and iron gluconate are parenteral forms of iron that are funded under the British Columbia Provincial Renal Medication Program The decision for which form to use is dependent on physician choice, patient tolerability and the evidence related to safety of each form

Iron dextran was the only form of parenteral iron available in the United States until 1999 It has proven efficacy but its safety has been questionable (Faich & Strobos, 1999) It has been reported that approximately 0 7% of iron dextran use in hemodialysis patients has resulted in life threatening anaphylactic reactions (Fishbane, Ungureanu, Maesaka, Kaupke, Lim, & Wish, 1996) Between 1976 and 1999, there were 30 deaths attributed to iron dextran use (Faich & Strobos, 1999) In a meta-analysis of studies of iron dextran use found drug intolerance rates of approximately 2 47% and anaphylaxis rates of 0 61 %, p< 0 0001 (Michael et al , 2002) It has been speculated that the high molecular weight dextran molecule rather than the iron itself induces anaphylaxis or contributes to adverse effects (Faich & Strobos, 1999, Michael et al , 2002, Sengolge, Horl, & Sunder-Plassman, 2005) Iron sucrose and iron gluconate (Ferrlecit) are increasingly being used in the hemodialysis setting due to the risk of serious adverse drug reactions related to iron dextran

Iron sucrose therapy is a safe alternative to iron dextran use In a summary of four prospective studies of 130 iron dextran or iron gluconate sensitive patients, no serious adverse events (anaphylaxis or death) occurred related to iron sucrose therapy in these same patients Fourteen non-serious drug related adverse events such as diarrhea, hypotension, nausea, vomiting and constipation occurred in 8 patients (Charytan, Schwenk, Al-Saloum, & Spinowitz, 2004)

Sodium ferric gluconate complex (iron gluconate or Ferrlecit) is a form of intravenous iron in which there is significantly less allergic and anaphylactic reactions occurring in comparison to iron dextran In a randomized controlled double blinded study of 2534 hemodialysis patients, there was a rate of immediate type of reaction of 0 04% (Michael et al , 2002) This indicates a statistically significant lower rate of anaphylaxis when compared to 0 61% in iron dextran use, p=0 0001 (Michael et al , 2002)

Target Hemoglobin Levels

Considering the impact of renal anemia on hemodialysis patients, several studies have looked at treatment and safety issues surrounding the use of ESAs For many years, the assumption in the nephrology community was that normalized Hgb levels presented positive outcomes for hemodialysis patients As a result, many studies were organized around this hypothesis

A systematic review of Hgb targets in renal anemia found that many studies hypothesized that higher Hgb levels were positively associated with improved survival The results indicate otherwise Of twenty-two randomized control trials involving 3707 patients, it was found that Hgb > 130 g/L was not associated with decreased risk of mortality when compared to Hgb levels of 120 g/L Lower Hgb targets of < 100 g/L resulted in increased risk of seizure (RR 5 25, 95% CI 1 13-24 34) and a decreased risk of hypertensive episodes (RR 0 05, 95% CI 0 33-0 76, Strippoli et al , 2006, p 1) The results regarding quality of life and higher Hgb values were inconclusive due to non-validated scales of assessment and "presentation of individual positive results instead of a generalized assessment useful for analysis" (Strippoli et al , p 8) The limitations of this review include the limited number of RCT's available, the small sample sizes in RCTs and the lack of primary end points at the patient level (Strippoli et al)

A meta-analysis of nine randomized controlled trials of various target Hgb of 5143 patients provided similar results (Phrommintikul, Haas, Elsik, & Krum, 2007) Higher Hgb targets demonstrated an increase of 20% in mortality, 30% in arteriovenous access thrombosis and 30% of poorly controlled blood pressure In this study, higher Hgb target levels were considered 120-160 g/L A sub-group of dialysis patients showed a relative risk of 1 11 (95 % CI 0 94-1 31, p=0 22) in the higher target Hgb group compared to the lower

Hgb group In addition, the risk of poorly controlled blood pressure was significantly higher in the high Hgb group than the low Hgb group (RR 1 27, 95% CI 1 08-1 50, p=0 004, Phrommintikul et al)

In 2006, two studies were published that resulted in the amendment of the National Kidney Foundation guidelines indicating an upper Hgb limit of 130 g/L The Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) trial studied 1432 patients with chronic kidney disease who were randomly assigned to receive epoetin targeted to achieve Hgb levels of 135 g/L or 113 g/L The primary end point was death, myocardial infarction, hospitalization related to congestive heart disease or stroke The results indicated that the higher Hgb group had a higher incidence of the primary end point and the trial was terminated early A target Hgb of 135g/L was associated with increased risk and no improvement in quality of life (Singh et al , 2006) Based on this evidence, the authors of the CHOIR study suggested that a target Hgb range of 110-120 g/L is based on lower risks and lower treatment costs

The Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin beta (CREATE) study randomly assigned 603 patients with Stage 3 or 4 chronic kidney disease to two groups with target Hgb levels of 130-150 g/L or 105-115 g/L The primary endpoint was eight cardiovascular events including sudden death, myocardial infarction, acute health failure, stroke, angina or cardiac arrhythmias with twenty four hour hospitalization, and peripheral vascular disease complications After three years, the CREATE researchers found that there was no significant difference between the two groups with regard to adverse events They concluded that normalization of Hgb in CKD anemic patients does not reduce the risk of cardiovascular events The CREATE study did find a slight increase in quality of life measurement in higher Hgb group (Drueke et al , 2006)

Both studies (Drueke et al , 2006, Singh et al , 2006) found that the event rates were higher among the participants that responded poorly to ESAs Some critics argued that the difference in event rates was most likely due to the high burden of disease among these poor responders as opposed to the variation of Hgb within the target range (Demirjian & Nurko, 2008, Greene et al , 2005) Other critics argued that a slight increase in quality of life is of significance to the patient and this should be considered on an individual basis (Muirhead, 2007) The conclusions from these studies suggest that Hgb > 130 g/L is not recommended due to increased risks of cardiovascular adverse effects The studies also indicated that there are positive effects to quality of life when normalization of Hgb occurs

A recent study on Hgb level variability did not find increased mortality among the above target range or even the higher end of target range (Gilbertson et al , 2008) Because this was an observational trial, its results have potential for more biases as compared to the CREATE and CHOIR randomized control trials and exert less influence over current treatment guidelines

Other studies have provided inconsistent results as they pertain to safe target Hgb ranges The Anemia in Chronic Heart Failure Outcomes and Resources utilization study (ANCHOR) found that the ESRD population with chronic heart failure with Hgb >170 g/L levels were at the highest risk of death, and the risk was reduced as the Hgb decreased to 130 g/L level (Go et al , 2006) A randomized controlled trial of 157 hemodialysis patients within a group of predialysis and peritoneal dialysis patients demonstrated that Hgb levels of 135-160 g/L improved quality of life as measured by decrease in fatigue, depression and frustration The incidence of thrombovascular events and vascular access thrombosis in hemodialysis patients did not differ between the lower and higher target Hgb (Furuland et al , 2003) A randomized, double blind study of the effect of normalized Hgb targets (Hgb 135-

145 g/L) on hemodialysis patients without symptomatic heart disease found that it has no beneficial effect on cardiac structure as evidenced by left ventricular volume index (Parfrey et al , 2005)

KDOQI guidelines from 2006 conclude that a Hgb lower limit of 110 g/L and an upper limit not > 130 g/L are the most efficacious in terms of disease management (National Kidney Foundation, 2006, p S33) On the basis of the CREATE and CHOIR studies, maintenance of Hgb levels >130g/L appears to require more epoetin, increasing costs to health care while placing patients at significant risk of adverse cardiovascular events (Steinbrook, 2006) Based on the wording of this guideline, no upper limit was determined except for avoiding Hgb >130 g/L This was considered an opinion-based guideline and has since been amended to an evidence-based guideline Current evidence supports a Hgb target range of 110g/L-120 g/L (National Kidney Foundation, 2007)

Normalization of Hgb levels is a complex issue in hemodialysis patients As reported by the United States Renal Data System Annual Report, 42% of patients reaching Hgb > 140 g/L, achieve this level within six months of reaching the target level of 110 g/L (National Institutes of Health, 2008) Lack of attention to the higher target Hgb levels may lead to overuse of ESAs, contributing to overshooting targets (Collins, Ebben, & Gilbertson, 2007) Indeed, overshooting the target Hgb level was 3 to 4 times more common in 2008 than it was in 1997 (Kapoian, 2008) Higher ESA doses is associated with decreased survival by reflecting resistance to ESA treatment within coexisting inflammation and malnutrition issues (Kalantar-Zadeh, Kopple, Block, & Humphreys, 2001, Locatelli et al , 2006)

Just as higher Hgb levels increase health risks for the hemodialysis patient, lower Hgb levels expose the patient to a greater risk In a study of 12 countries and dialysis outcomes, 23-29% of hemodialysis patients were below 110 g/L in Sweden, the United States, Belgium

and Canada (Pisoni et al , 2004) Hemodialysis patients with lower Hgb levels were potentially at the highest risk of mortality (Locatelli, Conte, & Marcelli, 1998)

Hyporesponsiveness to ESAs creates a challenge to maintain the minimum Hgb target level One study indicated that 75% of ESA hyporesponsive patients with a non-functioning arteriovenous graft had evidence of a bacterial infection without symptoms The only evidence of infection was higher ferritin levels with low Hgb levels, suggesting inflammation or infection can greatly influence anemia management (Nassar, Fishbane & Ayus, 2002)

Additional studies have addressed the challenge of maintaining Hgb levels within a narrow target range, indicating large variability in individual patient results (Berns et al , 2003, Lacson, Ofsthun, & Lazarus, 2003) "Achievement of Hgb within this target range is prone to fluctuation" (National Kidney Foundation, 2007, p 503), and is a common phenomenon in hemodialysis patients (Walker & Pussell, 2007) It has been reported that 90% of hemodialysis patients have cyclical Hgb results averaging 10 3 weeks and 25 g/L in range (Fishbane & Berns, 2005) The variability of Hgb levels observed in clinical practice indicates that 95% of hemodialysis patients using ESAs would obtain a Hgb interval range as high as 56 g/L (using a normal curve) (Berns et al , 2003) Hemoglobin variability can be influenced by the appropriateness of physician orders for ESA dose change, biological diversity within a population, unique patient responsiveness to ESAs, hemodilution related to fluid overload, adequacy of iron stores, bleeding, and inflammatory responses (Collins et al , 2005)

According to one study of Hgb variability, a typical hemodialysis patient can be expected to have 42% of 3 month rolling average Hgb values outside of the 110-120 g/L range (Lacson, Ofsthun, & Lazarus, 2003) Variability in results among hemodialysis patients will present transient Hgb levels >130 g/L and a temporary spike does not constitute

a safety concern when appropriate adjustments are made to ESAs (National Kidney Foundation, 2006) Related to intrapatient Hgb variability, Lacson et al (2003) suggest that a wider target range will reduce the likelihood of staff responding aggressively to Hgb levels and decreasing Hgb fluctuations

Variability of Hgb levels can be associated with increased mortality A one year retrospective study of 159,720 hemodialysis patients showed the degree of Hgb variability, low and highly variable levels were associated with increased risk of death (Gilbertson et al , 2008) Patients consistently within target hemoglobin levels, as well as those persistently over target, had lower mortality rates (Gilbertson et al) These results speak to the necessity of ensuring best outcomes for patients by maintaining Hgb levels within acceptable range

Examining Hgb results require monitoring of longitudinal trends to prevent sudden reaction to isolated Hgb values, taking into account changes in a patient's condition such as infection or hospitalization (Breiterman-White, 2003) A single Hgb level often reflects a range of ESA doses over a period of time (Locatelli, Del Vecchio, & Pozzoni, 2007, National Kidney Foundation, 2007) Withholding ESAs for a Hgb level greater than target range contributes to unpredictable and variable Hgb levels downward Incrementally decreasing EPO doses provides effective clinical results as opposed to holding doses which can result in plummeting Hgb levels (Breiterman-White)

There is an association between Hgb levels and hospitalization In a prospective observational study of 11,041 hemodialysis patients from 7 countries, results concluded that the risk of hospitalization decreased 9-55% over 5 years in patients with Hgb 110-120 g/L (Pisoni et al , 2004) In a study of U S hemodialysis patients treated with ESAs, Hgb levels dropped 5 3 g/L within 30 days of hospitalization as compared to 3 months prior and this was statistically significant ($p< 0\ 001$, Pisoni et al) It is evident that patients who are

hospitalized can experience more pronounced anemia Pisoni et al demonstrated that mortality and hospitalization risks decreased by 5-6% for every 10 g/L increase in Hgb level up to target range

Clinical Decision-making

Clinical decision-making is an essential skill that impacts the nurse, patient and institution The quality of clinical decision-making determines the delivery of nursing care and the quality of patient outcomes (Arries, 2006) Each nurse brings unique knowledge to a clinical problem and this plays a role in how a problem is interpreted and which clinical issues will be attended to (Jones, 1988 as cited in Bakalis & Watson, 2005) Clinical decision-making can also impact an institution The quality of a nurse's decision-making influences the outcome for the patient which can financially impact an institution (Arries) Because of the diversity of nursing, education, knowledge and experience in any health care institution, standardization of patient care can assist in providing better patient outcomes

The role of the registered nurse (RN) has become more complex as changes to the health care system demand increased responsibilities for the care of the patient An emphasis on cost-effectiveness in conjunction with increased disease chronicity requires highly qualified, accountable individuals who accept responsibility for decision-making about patient care (Mrayan, 2003) A strategy to control costs while maintaining quality of care is to expand the scope of activities of the nurse Transferring medical management of a specific clinical issue creates an environment where nursing has greater responsibility and accountability for patient care (College of Registered Nurses of British Columbia, 2008) The College of Registered Nurses of British Columbia (CRNBC) strongly encourages employers to develop decision-making tools to assist nurses in their clinical practice as responsibilities and activities expand In BC, health care employers are responsible for the

development and initiation of any clinically-based client decision making tool that nurses use (CRNBC, 2008)

Decision-Making Tools

Clinical protocols are based on a standardized approach to practice and derive its origins from algorithms (Ilott, Booth, & Patterson, 2010) A clinical algorithm is a set of logical, sequential steps shown as a decision tree which directs patient care (Gerdtz & Bucknall, 1999, Miller, York, & Ryan, 2005) An algorithm in the clinical setting is linear in approach to clinical problem solving, displaying major decision points in disease management and strategies of action (Department of Veteran Affairs, 2002, Schwartz & Griffin, 1986) Using a specific, logical approach to clinical problem solving is essential to decision-making and can assist in the assessment of the patient (Department of Veteran Affairs, 2002)

Algorithms and/or protocols which incorporate clinical practice guidelines provide a framework for evidence-based care within a specialty Within the nephrology specialty, the KDOQI clinical practice guidelines and recommendations are the standard guidelines for all stages of chronic kidney disease (National Kidney Foundation, 2006) Algorithms within a specialty cover the scope of a guideline to provide a summary of appropriate management decisions and strategies to address specific patient issues (Hadorn, 1994) Ideally, an algorithm is the translation of research into functional interventions, using a problem solving orientation to create steps grounded in evidence-based principles and practice (Miller et al , 2005)

The advantages of clinical algorithm use in practice relates to its impact on patients, clinical practice, and institutions Algorithms can assist nurses to identify when testing is unwarranted and as a result provides more efficient patient care (Hadorn, 1994) Algorithm

use in clinical practice can improve patient safety related to standardization of care regardless of size or geographical remoteness of practice site (McDonald, 2007) Reducing variations by standardizing clinical practice is effective in minimizing the probability of error in judgment (Kohn, Corrigan, & Donaldson, 1999), thus placing the nurse at lower professional practice liability risk (Bucknall & Thomas, 1995, Gerdtz & Bucknall, 1999) Algorithms reduce the risk-adjusted outcomes for an organization by reducing the risk of medication error (Vanhaęcht, de Witte, & Sermeus, 2007) Within an organization, algorithm use provides a basis for establishing autonomy of practice within a safety net of mutually agreed upon actions

Limitations of clinical algorithms are well-documented "The systematic use of algorithm approaches has the potential to hinder development of more flexible approaches to problem solving" (Gerdtz & Bucknall, 1999, p 55) It can be important to look outside the decision-making tree to find solutions that may apply to a specific patient or clinical situation Perhaps the most imminent concerns with using algorithms are having clinical practice dictated, losing control of practice and being monitored by others (Hartigan et al , 2003) Another drawback is the time required to delineate all of the information in the algorithm, much of which does not apply to the patient at hand (Hadorn, 1994) Other criticisms of algorithms are the questionable clinical validity of some recommendations, which are not always linked to best guideline practices or systematic reviews (Hadorn)

Renal Anemia Management Protocol (RAMP)

A RAMP is a type of algorithm that provides standardization of care in a hemodialysis unit The primary components of an anemia management protocol include target Hgb levels, defined parameters for use of ESAs and intravenous iron, defined and corrective actions related to causes of a hyporesponse, and clear documentation of

assessments, interventions and outcomes (Michael, 2005) The measure of success of any anemia management protocol is its ability to guide clinical interventions to ensure every patient has the same standard of care If these components are directed by evidence-based guidelines, the achievement will be improved patient outcomes and organizational efficiency

When examining the use of protocols in the management of anemia in hemodialysis patients, the evidence points to its benefits "Increased utilization of anemia management algorithms to guide treatment decisions for ESAs and iron therapy can allow a range of renal care professionals, in acute and primary care settings, to deliver consistent and effective treatment of patients to recommended hemoglobin target" (Macdonald, 2007, p 185) Renal anemia management using a treatment algorithm can reduce variability of Hgb levels by implementing best practices and routine Hgb assessments in the care of the patient (Breiterman-White, 2003, Lacson, Ofsthun & Lazarus 2003) Standardized care and reduction of variability in Hgb levels are essential to producing positive patient outcomes in the hemodialysis population

The use of a standardized anemia protocol in the nephrology setting has the potential to impact patient outcomes In a recent study of target Hgb levels and risk of hospitalization, those patients with more months below target range were less likely to have received intravenous iron and were more likely to be hospitalized or die (Ishani et al , 2008) A lack of appropriate and timely anemia treatment could be avoided with the use of a renal anemia management protocol "Institutional variability in anemia care is a potentially modifiable factor associated with the inability to achieve target hemoglobin concentrations" (Ishani et al , p 1686)

Anemia management protocols are used extensively in North America with varying results related to target Hgb and ESA use A study of facility factors which affect the

achievement of target Hgb found that although the protocol was effective in the initial management of anemia management, maintenance and refinement of the protocol were a necessary step to improving target ranges (Chan, Lafayette, Whittemore, Hlatky, & Moran, 2008) In a randomized controlled trial of an anemia management protocol in hemodialysis patients, the use of erythropoeitin was substantially reduced with no improvement in the achievement of target Hgb levels (Brimble, Rabbat, McKenna, Lambert, & Carlisle, 2003) A study of hemodialysis patients in the Northern Alberta Renal program found no significant change in anemia pre-implementation to an algorithm versus post-implementation with a noted concern regarding the adherence of the algorithm throughout the study (Nhan, Jensen, & McMahon, 2007) Collins et al (2007), analyzed the likelihood of Hgb above target levels related to practice patterns Patients with Hgb > 130 g/L were assessed to determine if appropriate dose reduction in ESAs was prescribed in the month following change in Hgb level It was reported that approximately 70% of dialysis providers followed KDOQI guidelines, but this was often dependent on whether a dialysis facility was owned by a corporation, or it was hospital-based Hospital based dialysis facilities complied with guidelines more often Although anemia protocols may reduce ESA use and thus reduce costs to a health care institution, patient outcomes have not consistently improved, at times dependent on individual clinical practice and expertise in the application of these tools

Protocol-based care by renal nurses has potential benefits of providing direction and structure for practice to the novice nurse, while enabling autonomy in decision-making to manage anemia in the hemodialysis patient It also creates an environment of critical thinking for the nurse to use the KDOQI guidelines for anemia, iron and ESA and assess how the interaction of these indices determines and guides decisions (Breiterman-White, 2003) Many dialysis facilities develop anemia management protocols to guide ESA dosing where

there are limitations to available physician and nursing time to provide anemia management (Weiner & Levey, 2007) In addition to efficiently using ESAs, protocol use can assist the nurse to identify patients who are hyporesponders (Demirjian & Nurko, 2008) Protocols can contribute to the efficacy of resources such a lab testing

Evaluating Patient Outcomes

Outcomes assessment is a necessary component of nursing care because it provides evidence for accountability of practice (Irvine, Sidani, & McGillis Hall, 1998) Donabedian introduced the model of health care quality using structure, process and outcomes as three quality determinants of health care (Donabedian, 1966) The Donabedian model has influenced the development of theories and models to delineate nursing outcomes research Donabedian's model focuses on the quality of health care by examining the structure of the environment and the processes that result in measurable outcomes Originally, this framework influenced studies on cost, length of stay, patient mortality, and patient satisfaction (Doran, 2003) It has now been used to address patient outcomes which can be sensitive to nursing care within a variety of health care settings (Doran)

Those outcomes that are nursing sensitive are "relevant based on nurses' scope and domain of practice and for which there is empiric evidence linking nursing inputs and interventions to the outcome" (Doran, 2003, p vii) The National Quality Forum (NQF) (2004) defines nursing sensitive outcomes as outcomes that are affected, provided and /or influenced by nursing personnel, but for which nursing is not entirely responsible The relationship between nursing actions and nurse sensitive outcomes is "quantifiable but not necessarily causal" (National Quality Forum, 2004, p 2)

The development of nurse sensitive outcomes began in the 1990's as a result of media and scientific studies identifying decreased quality of patient care and outcomes (Needleman,

Kurtzman, & Kizer, 2007), as well as the shortage of nurses within the health care system (National Quality Forum, 2004) As a result of concerns regarding quality of care and nursing human resource shortages, many nursing outcomes studies have focused on nurse staffing, prevention of adverse events and patient safety (Aiken, Sochalski, & Anderson, 1996, Aiken, Clarke, Sloane, Sochalski, & Silber, 2002, Cho, Ketefian, Barkauskas, & Smith, 2003) Many studies have demonstrated the correlation between nurse staffing, processes of care and patient outcomes In a meta-analysis of 28 studies, there was an association between RN–to-patient ratio and patient mortality and adverse effects (Kane, Shamliyan, Mueller, Duval, & Wilt, 2007) The link to negative outcomes such as adverse effects, complications or mortality is the most published area of nursing outcomes research (Doran, 2003) There is a gap in nursing research in the area of studying nursing actions that demonstrate positive patient outcomes instead of avoiding negative outcomes

Additional challenges in nursing outcomes research are related to the limited evidence directly linking patient outcomes to nursing activities in acute care settings A review of 4000 systematic reviews and 500 meta-analyses on nursing interventions and patient outcomes in acute care settings found that there is limited evidence to establish a direct association between nursing actions and patient care outcomes (Bolton, Donaldson, Rutledge, Bennett, & Brown, 2007) For example, patient satisfaction is identified as a nurse sensitive patient outcome (Doran, 2003) despite its vague definition Patient satisfaction appears to be patient specific, influenced by factors such as affective response and lack of standardized measurement Bolton et al (2004) strongly encouraged the development of standardized nursing interventions and patient outcomes to test the efficacy of nursing interventions across a patient population

Nursing sensitive care can be categorized into three areas (National Quality Forum, 2004) First, patient-centered outcome measures are those outcomes of care delivered to patients by nurses They can include failure to rescue, falls, restraints, pressure ulcers, central line infections and urinary tract infections from catheters Second, nurse-centered intervention measures focuses on aspects of nursing intervention and processes of care, such as nicotine counseling Third, system-centered measures focus on organizational effectiveness that influences and is influenced by nursing care System centered measures are represented by skill mix, nursing care hours and nurse turnover There are limited standardized nurse sensitive measures which are applicable in the nephrology nursing setting

Within the nephrology specialty, nurses are in a key position to influence patient-centered outcomes Nephrology nurses are instrumental in improving anemia treatment and resultant outcomes because of their coordinating role in the care of the hemodialysis patient, working to reduce the clinical symptoms of anemia and thus influencing renal and cardiovascular health (Macdonald, 2007, Singh & Hertello, 2005) Nephrology nurses are actively involved in data collection and patient assessments, enabling identification and management of anemia (Bennett & Alonso, 2005) The use of a RAMP to produce target Hgb levels can be utilized to test of the efficacy of nurse-driven anemia management across the hemodialysis population

There remains a need for nursing research to contribute to a greater understanding of the unique interventions of nursing and the impact these actions have on quality patient outcomes It is often difficult to separate the contributions of nurses from those of physicians and other health care providers (Naylor, 2007, Needleman, Kurtzman, & Kizer, 2007) Nursing actions are often intertwined with others' actions within the health care team

Determining actions unique to the nursing role can validate nurses' contribution to patient care

Nursing Role Effectiveness Model

The Nursing Role Effectiveness Model (NREM) was developed based on the Donabedian model (1966) to address the need to measure quality nursing care (Doran, 2003) The NREM (Figure 5) provides a framework to delineate the relationship between structure, process and outcomes within the context of nursing (Doran et al , 2006) This model groups nursing roles into three categories and links these roles to nurse-sensitive patient outcomes

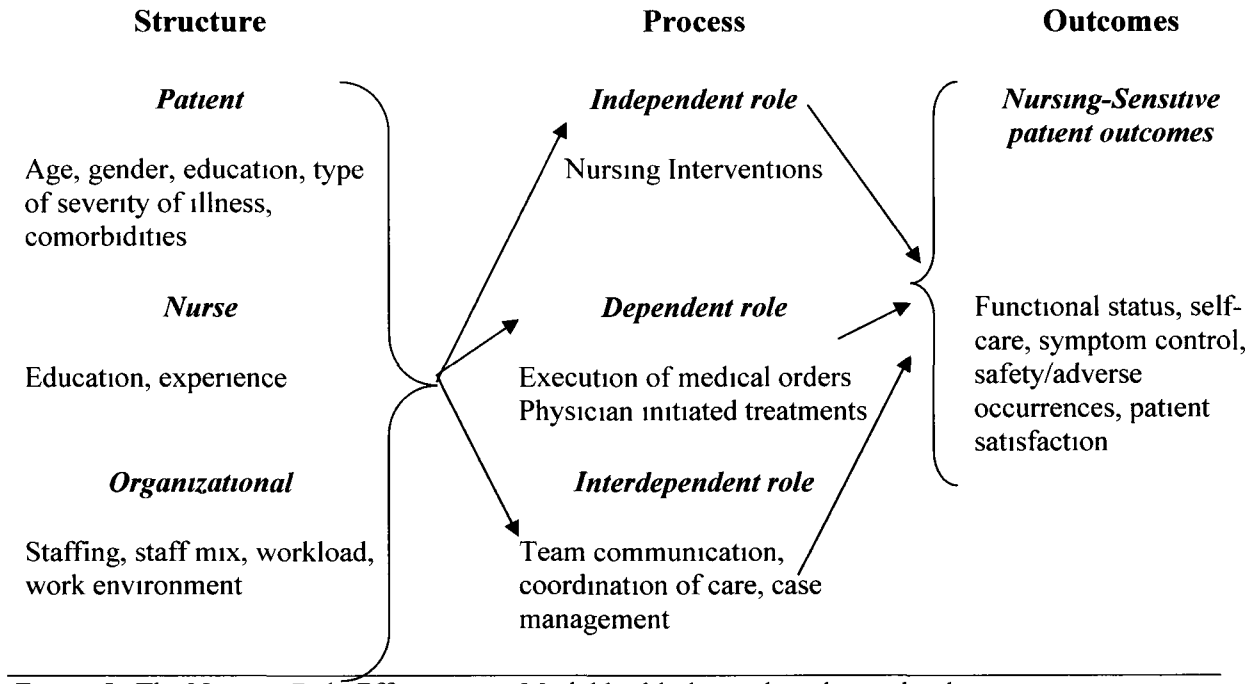

Figure 5 The Nursing Role Effectiveness Model highlighting the relationship between structure, process and outcomes Adapted from The Nursing Role Effectiveness Model (Irvine, Sidani & McGillis Hall, 1998)

The structure component consists of patients, nurses, and organizational variables that impact processes and outcomes of care (Doran, Sidani, Keating, & Doidge, 2002) Patient variables such as diagnosis, severity of illness, and co-morbidity can influence patient outcomes Nurse variables can include number of years experience, educational background

and clinical skills Organizational variables are those measures that emphasize nursing staff ratio, workload measurement and assignment patterns

The process component identifies three roles of the nurse and categorizes these roles based on the functions or activities of the nurse, independent, dependent, interdependent roles The independent role includes those role functions such as patient assessment, decision-making, and intervention for which only nurses are responsible The nurse's dependent role includes clinical actions and judgments involved in the implementation of physician's orders and/or medical treatments The interdependent role encompasses all functions and responsibilities which nurses share with other health care professionals such as inter-professional communication and coordination of team-based patient care

The outcome component of the model consists of nurse-sensitive patient outcomes Nurse-sensitive patient outcomes are those changes that occur in the patient as a result of nursing interventions (Doran, 2003) such as patient's health status, patient's perception of nursing care, and direct/indirect costs related to nursing care

The NREM provides a framework for the study This study examined the relationship between structure, process and outcomes in renal anemia management Patient structural variables including age, gender, race, diagnosis, location of dialysis, number of days of dialysis, number of days of hospitalization, and co-morbidities influenced process and outcomes variables There are no nursing or organizational structural variables examined in this study

The process variables differ between the control and protocol groups The control group nurses enact a dependent role to provide medically directed renal anemia management to hemodialysis patients The protocol group nurses worked within the independent role by using a nurse-driven protocol to provide renal anemia management to hemodialysis patients

The protocol group nurses also worked within the interdependent role when communication with the nephrologist or renal pharmacist was required according to protocol guidelines The differing process variables in either the control or protocol groups may have influenced the outcomes of the study

Outcome variables in this study were represented by clinical lab values, dosage use of ESAs and intravenous iron, and cost of ESA and iron use The primary patient outcome examined in this study was Hgb levels This study also examined whether or not Hgb levels could be considered a nurse-sensitive patient outcome Other patient outcomes that were assessed in this study are transferrin saturation levels, ferritin levels, ESA use, and intravenous iron use

CHAPTER 3

Methods

This study design was framed by the Nursing Role Effectiveness Model, illustrated in Figure 5 and discussed in the previous chapter In this study, renal anemia was managed by the nurse in two different ways The control group hemodialysis nurses utilized physician's orders to manage renal anemia (physician-driven approach) In contrast, the protocol group nurses functioned independently in decision making, assessment, intervention and follow up to provide care to renal anemia patients using a RAMP (nurse-driven protocol) An examination of the control and protocol groups was completed by using a case/control study design This study design was chosen to provide a comparison of two groups to evaluate clinical patient outcomes and costs of a nurse-driven protocol approach to renal anemia management in contrast to an established physician-driven approach to anemia management

Study Design

A retrospective, non-equivalent case control group design was used to determine whether the process of using a nurse-driven RAMP was associated with equally effective patient outcomes when compared to a physician-driven anemia management approach The study time interval for the control group was October 2005-October 2006 The study time period for the NRP was from October 2007-October 2008 Using two groups from different settings was intended to increase the representativeness of the results

Sources of Data

This study used data collected and maintained by the British Columbia Provincial Renal Agency (BCPRA) from the Patient Record/Registration and Outcome Management Information System (PROMIS) database The BCPRA is under the Provincial Health Services Authority It is an agency that improves the health of individuals in British

Columbia with kidney disease by implementing province-wide solutions to the specialized needs of renal patients in collaboration with BC health authorities and community partners BCPRA manages personal health information under the BC Freedom of Information and Protection of Privacy Act (FOIPPA)

PROMIS is the health information system for the BCPRA and the only province-wide integrated registry for renal patients in Canada This database incorporates extensive demographic and clinical data on all hemodialysis patients in BC Data collected from renal units provides information for patient management, renal unit management, research, continuous quality improvement, and outcomes-based planning (British Columbia Provincial Renal Agency, 2009a) It incorporates clinical tools to support direct patient care in addition to supporting resource allocation The BCPRA uses PROMIS to provide an information link between renal health care professionals and the renal care community in British Columbia

The PROMIS database provides patient-specific information such as patient demographic information, treatment characteristics, underlying chronic conditions causing CKD, date of registration, lab data, and medication profiles Unit clerks in the regional hemodialysis units enter this information into the PROMIS database for all BC hemodialysis patients

Sample

A non-probability sample of eligible participants was drawn from all hemodialysis patients in the NRP on the RAMP and all hemodialysis patients in the KRP not on a protocol The control group consisted of a sample of hemodialysis patients (n=64) with renal anemia in the KRP for a 1-year period in which a standardized nurse administered anemia management protocol was not in use The protocol group included all hemodialysis patients (n=43) in the NRP that were evaluated and treated using the RAMP Using the information available from

the NRP hemodialysis unit records, a list of those patients who were treated using the RAMP in October 2007 was compiled by the renal pharmacist This list, in addition to personal health numbers, was sent electronically to the BCPRA There was no disclosure of this list or information to the researcher or any party other than the BCPRA After the list had been sent, the BCPRA also received an electronic list of exclusion and inclusion criteria, as well as variables to study, from the researcher Matching by gender, age and diagnosis was not possible due to a limited number of patients eligible for the study Figure 6 illustrates the selection process to determine eligibility of the control and protocol groups for the study

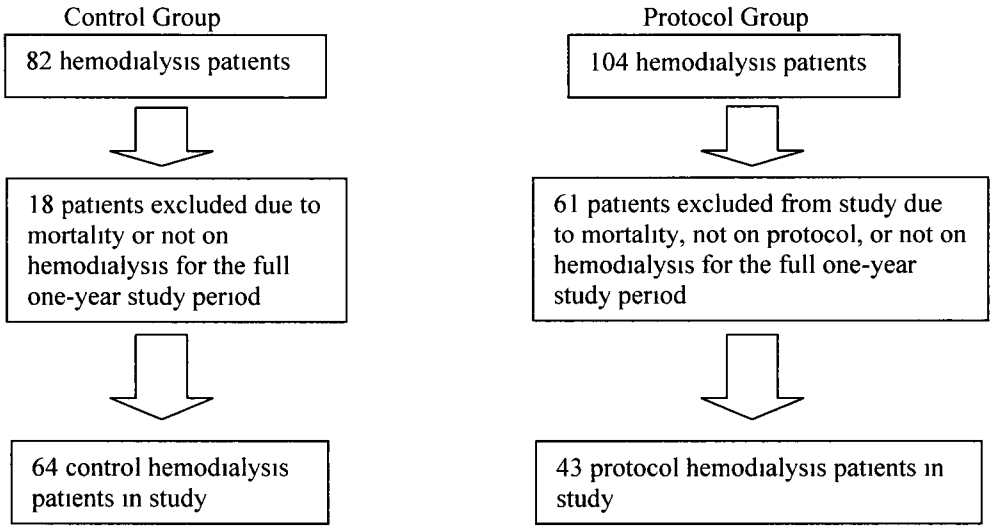

Figure 6 Selection process for control and protocol groups

All patients that died at any period during the study were excluded All chronic hemodialysis patients registered with the BCPRA and who had Hgb levels and at least one transferrin saturation reading in the database were included in the study

Study Variables

To provide descriptive comparisons of the control and protocol groups, data regarding the following variables were examined age, gender, race, diagnosis, co-morbidities, location of dialysis treatments, and length of time on dialysis Patient outcomes were measured

clinically by lab values and dosages of renal anemia medications such as ESA and intravenous iron

The lab data specific to this study were Hgb, transferrin saturation, and ferritin levels Hemoglobin is the protein component of the red blood cell The Hgb was measured as g/L in this study Hemoglobin lab values were measured monthly for each patient Transferrin saturation is a lab value that indicates the amount of transferrin attached to iron and it is measured in percentage For this study, transferrin saturation was the primary measurable indicator of available iron in a patient The transferrin saturation level was measured every three months Ferritin levels were also used as an iron indicator Ferritin levels were measured intermittently based on need for assessment of iron status in the patients

Renal anemia medications were evaluated based on patient usage A patient's ESA requirement was defined as the monthly dose of ESA, either Epoetin alfa or Darbepoetin alfa, administered during the study The intravenous iron requirement was defined as the monthly dose of iron, either iron dextran, iron saccharate (iron sucrose), or ferrous gluconate (ferrlecit) administered during the study

Data Analysis

Data was analyzed using SPSS 17 0 software Descriptive baseline statistics of gender, race, age, diagnosis, days of hospitalization, co-morbidities, and duration of hemodialysis were presented using *n*, means and/or standard deviations for the control and protocol groups To determine if significant differences existed between groups in Hgb levels, *t*-tests were completed Repeated measure testing was not feasible as there were missing data in the protocol group, limiting the number of consecutive monthly Hgb readings available for this test Additional data analysis was conducted using chi square test for categorical Hgb levels Transferrin saturation levels were compared in each group using

means and *z*-scores to determine the rate of patients reaching target levels Ferritin levels were compared using means and relating these values to standard guideline target ferritin levels A comparison of intravenous iron use per month for each group was completed by averaging the overall use of iron To determine the differences between the mean dose of ESAs between the control and protocol groups, a *t*-test was performed The cost of intravenous iron use on a monthly basis was calculated by multiplying the mean dose of iron each month per group and the iron cost per mg The cost of epoetin alfa was calculated by multiplying the average per-person monthly dose and the epoetin alfa cost per unit

Cost Effectiveness

A comparison of cost effectiveness of the two approaches to anemia management involved reviewing the control and protocol groups' usage of renal anemia medications Evaluation of the costs of intravenous iron and ESA's enabled the researcher to provide a comparison of the groups Calculating costs included determining the total average monthly dosage of epoetin alfa per person and multiplying by the cost per unit dose The costs of intravenous iron were calculated based on the average monthly dose of the group multiplied by the cost per mg The cost per unit of medication is based on the BCPRA summary of monthly costs of medications (2009) available on the BCPRA website (BCPRA, 2009)

Ethics

Aggregate data from the BCPRA PROMIS database was utilized for this study Consent for the use of any data in the PROMIS database was signed at initial point of renal care in British Columbia (Appendix B) and therefore every patient in this study had a signed consent Preliminary permission to use this database was granted to the researcher pending ethics approval (Appendix C) Ethics approval was granted by the University of Northern

British Columbia Research Ethics Board and the Northern Health Research Review committees (Appendices D & E)

This study consisted of the "secondary use of information that was anonymous, anonymized or de-identified/coded and where the research team had no access to the code"(Canadian Institutes of Health Research, Natural Sciences and Engineering Council of Canada, Social Sciences and Humanities Research Council of Canada, 2008, p 49) There was no possibility of patient contact as all the data necessary were present in this database and sent to the researcher in codified form No personal information could be re-identified by the researcher after coding had occurred and therefore the privacy of the participants was protected

All data was secured in a locked filing cabinet or by means of secure password-protected electronic data files Destruction of files and database information generated for this study will take place no later than five years after data collection All paper-based information will be shredded while all computer-based information will be deleted five years after study completion Information for dissemination of results (presentation or publication) will be provided in a non-identifiable format to ensure the anonymity of subjects

Procedures

This study was conducted using the RAMP from NRP as an intervention in the protocol group The RAMP transfers anemia management of hemodialysis patients to nurses upon order of the nephrologist (Appendix A) This protocol was implemented as a unit-wide policy change in anemia management in the NRP All nurses were trained to use the protocol by attending two training sessions One of the sessions included a guest speaker from Fraser Health Authority A review of case studies with a resource nurse and a pharmacist provided

an opportunity to demonstrate the use of the protocol There was no dedicated protocol resource nurse available so nurses were working in pairs to use the RAMP

All patients had monthly lab work drawn on a designated date to monitor Hgb levels The lab work also included iron studies indicated by transferrin saturation (TSAT) and ferritin levels at beginning of protocol, every three months thereafter and as needed Depending on Hgb status, the protocol provides step-wise instructions on how to titrate an erythropoietic stimulating agent (ESA) or provide iron therapy Steps for monitoring Hgb status were also provided in the protocol If the Hgb was 126 g/L or higher with a >20 g/L increase since last Hgb, the physician was notified The targeted Hgb for this protocol was between 110-125 g/l Transferrin saturation level was targeted between 20% and 50% Ferritin levels were drawn every three months and as needed These targets were agreed upon by the protocol committee based on the KDOQI guidelines at the time of printing

CHAPTER 4

Results

Comparison of Control and Protocol Groups

This study presented two groups in comparison The control group consisted of hemodialysis unit patients from three centres in the KRP, Kelowna General Hospital (KGH), Rutland, and Vernon, treated without a RAMP The protocol group consisted of hemodialysis patients from three centres in the NRP, University Hospital of Northern British Columbia (UHNBC), Fort St John, and Terrace Northwest, treated using a RAMP Throughout this chapter, the control group data will be presented first This will allow a clear comparison of the group without the use of a RAMP to the protocol group Table 4 shows the distribution of patients in each group

Table 4
Distribution of Patients in the Control and Protocol Groups

	Group	*n*	Percent
Control	KGH	27	42 2
	Rutland	16	25 0
	Vernon	21	32 8
	Total	64	100 0
Protocol	UHNBC	29	67 4
	Fort St John	7	16 3
	Northwest	7	16 3
	Total	43	100 0

Classification of descriptive data in the control and protocol groups is shown in Tables 5, 6 and 7 Table 5 includes a brief summary of patient demographic characteristics of gender, age and race data The term gender was defined as a patient's biological sex Caucasian and First Nations groups are displayed as these are the predominant races in each group Table 6 shows the age distribution of patients in each group

Table 5
Gender, Race, and Age of Patients in Control and Protocol Groups

Variable	Control	Protocol
Gender n (%)		
Male	34 (53 1)	30 (69 8)
Female	30 (46 9)	13 (30 2)
Age (yrs)		
Mean ± SD	62 0 ± 15 4	61 6 ± 13 8
Range	64	65
Race n (%)		
Caucasian	51 (79 7)	29 (67 4)
First Nations	2 (3 1)	12 (27 9)

Note Values enclosed in parentheses indicate percentage

Patients in the control group (n=64) had a mean age of 62 0 with a standard deviation of 15 4 years Approximately 84% of all the patients in the control group were in the age bracket of 41-80 years old The protocol group (n=43) had age data very similar to the control group with a mean age of 61 6 years and a standard deviation of 13 8 years The age distribution of the protocol group was very similar to the control group with approximately 84% of all patients in the age bracket of 41-80 years old

Table 6
Age Distribution of Control and Protocol Groups

Age (years)	Control	*n*(%)	Protocol	*n*(%)
11-20	1	(1 6)	0	(0)
21-30	2	(3 1)	1	(2 3)
31-40	2	(3 1)	3	(7 0)
41-50	9	(14 1)	5	(11 6)
51-60	12	(18 8)	11	(25 6)
61-70	13	(20 3)	12	(27 9)
71-80	21	(32 8)	9	(20 9)
81-90	4	(6 3)	1	(2 3)
91-100	0	(0)	1	(2 3)

There were significant differences between the groups for gender split or diagnosis There was a considerably greater percentage (70%) of males in the protocol group (Figure 7), while there was an approximate gender split of 50% in the control group Race data

indicated large differences between the groups The protocol group had almost a third of its patients identified as First Nations while the control group had less than 4% (Figure 8) The control group had approximately 10% of patients in an unidentified other race category

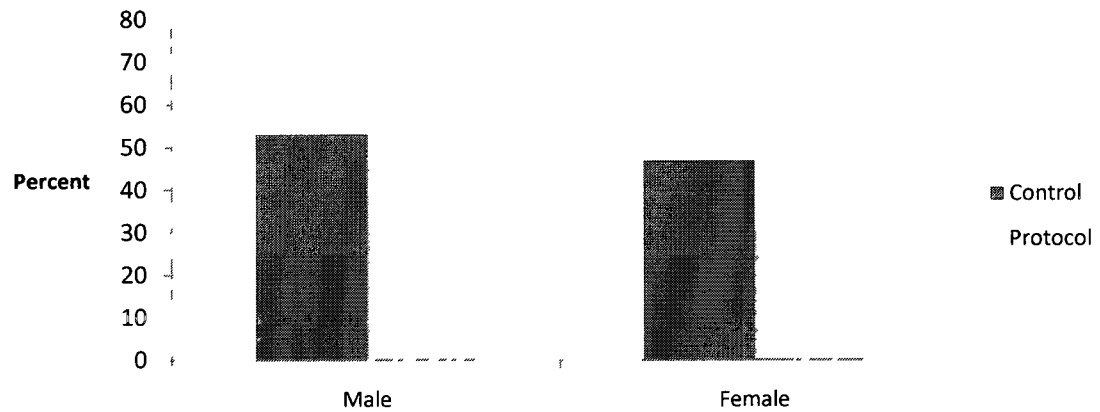

Figure 7 Comparison of gender split in control and protocol groups

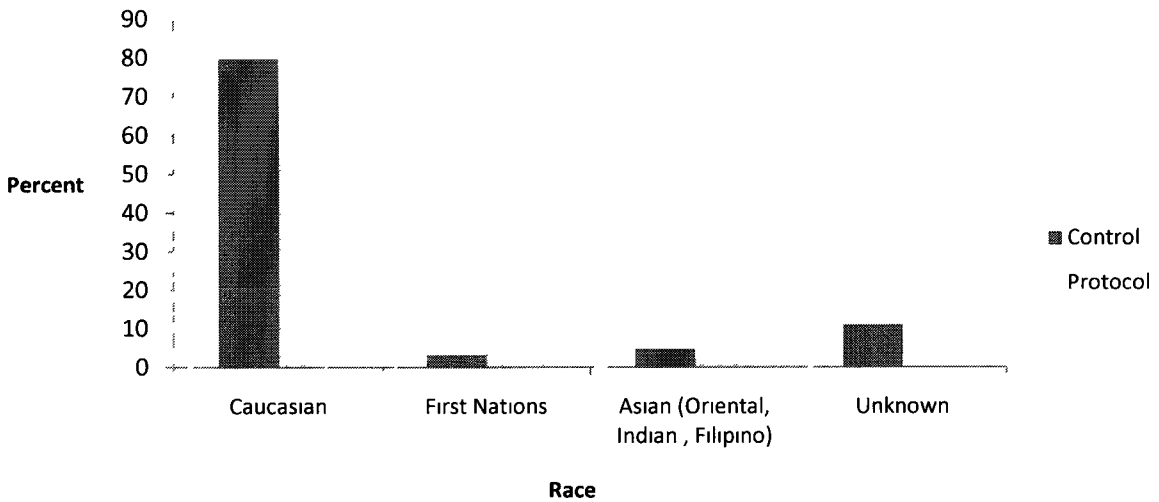

Figure 8 Comparison of race in control and protocol groups

Hospitalization days, hemodialysis days, diagnosis and co-morbidity data are presented in Table 7 The hospitalization data are measured by days hospitalized during the study Hemodialysis days pre-study are displayed as mean days Diagnosis was categorized

based on the most prevalent causes of kidney disease with an "other" category which did not identify a specific diagnosis in the database Co-morbidities were also reported as frequency and percent incidence

Table 7
Hospitalization, Hemodialysis Days, Diagnosis and Co-morbidities for the Control and Protocol Groups

Variable value	Control	Protocol
	Days of Hospitalization	
0 days n (%)	33 (51 6)	19 (44 2)
1-20 days n (%)	19 (29 7)	14 (32 6)
> 21 days n (%)	12 (18 7)	10 (23 2)
	Hemodialysis days pre study	
Median	882	790
Mean	1235	1222
1-500 days	23 (35 9)	14 (32 6)
501-1000 days	14 (21 9)	14 (32 6)
1001-1500 days	9 (14 1)	7 (16 3)
1501-2000 days	8 (12 5)	3 (7 0)
2001-2500 days	4 (6 3)	2 (4 7)
>2500 days	6 (9 4)	3 (7 0)
	Diagnosis	
Diabetic Nephropathy	15 (23 4)	21 (48 8)
Renal Vascular disease	15 (23 4)	6 (14 0)
Chronic Renal Failure	13 (20 3)	5 (11 6)
Polycystic Kidney Disease	3 (4 7)	2 (4 7)
Glomerulonephritis	3 (4 7)	3 (7 0)
Obstructive Uropathy	1 (1 6)	2 (4 7)
IgA Nephropathy	1 (1 6)	2 (4 7)
Other	13 (20 3)	2 (4 7)
	Comorbidity	
Diabetes	19 (29 7)	28 (65 1)
LVH	37 (57 8)	34 (79 1)
CHF	40 (62 5)	40 (93 0)
CVA	43 (67 2)	41 (95 3)
MI	44 (68 8)	41 (95 3)
DYSL	13 (20 3)	15 (34 9)
HTN	52 (81 3)	41 (95 3)

Note LVH-=left ventricular hypertrophy, CHF=Congestive Heart Failure, CVA= Cerebrovascular Accident, MI=Myocardial Infarction, DYSL= Dyslipidemia, HTN= Hypertension

Nearly 50% of patients in the control group were not hospitalized during the study period Over 70% of the patients had 1500 hemodialysis days or less pre-study Diabetic nephropathy, renal vascular disease and chronic renal failure were the leading primary diagnoses for the group, with just over 20% incidence respectively The control group had approximately 20% of patients within the "other" diagnosis category The primary co-morbidity of the control group was hypertension (81 3%) Myocardial infarction and cerebral vascular accident were present in just over two-thirds of the patients in the control group

Approximately 45% of patients in the protocol group had no hospitalization days Over 80% of patients had 1500 hemodialysis days or less Nearly 50% of the protocol group had a primary diagnosis of diabetic nephropathy The protocol group had about 10% less incidence of renal vascular disease and chronic renal failure compared to the control group The protocol group had a high incidence of cardiac co-morbidities Over 90% of patients in the protocol group had hypertension, myocardial infarction, cerebral vascular accident and congestive heart failure identified as co-morbidities

The control and protocol groups were similar in total hospitalization days, number of hemodialysis days pre-study, and incidence of some primary diagnosis The percentage of patients with no hospitalizations days at 51 6 and 44 2 percent for control and protocol groups respectively were not importantly different (Table 7) Most of the patients in both groups had less than 1000 days of hemodialysis with similar mean days of over 1200 days The median hemodialysis days pre-study differed for the control and protocol groups at 882 and 790 days respectively Both groups had similar incidence of polycystic kidney disease, glomerulonephritis, obstructive uropathy, and IgA nephropathy

Based on diagnosis and co-morbidity incidence, there are considerable differences The control group had approximately 25% less incidence of diabetic nephropathy compared to the protocol group (Table 7) The control group had a 9% greater incidence of renal vascular disease than the protocol group The protocol group had over 90% of patients with cardiac co-morbidities such as myocardial infarction, congestive heart failure and left ventricular hypertrophy compared to the control group with approximately 30 % less incidence (Figure 9) The protocol group had over 30% more incidence of diabetes as a co-morbidity compared to the control group (Figure 9)

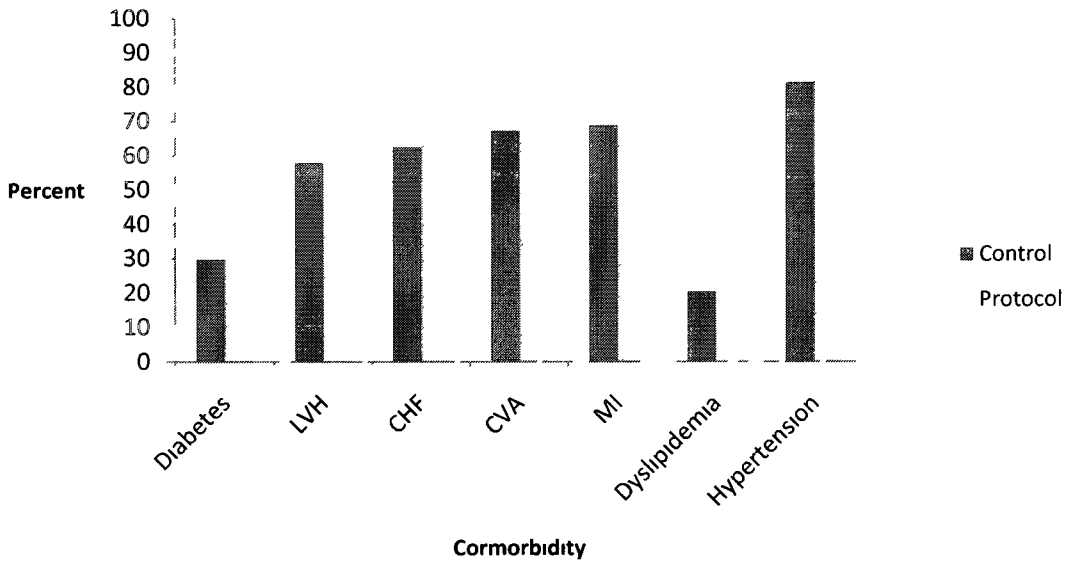

Figure 9 A comparison of incidence of co-morbidities in the control and protocol groups
Note LVH- Left Ventricular Hypertrophy, CHF- Congestive Heart Failure, CVA- Cerebrovascular Accident, MI- Myocardial Infarction

Data Analysis

Outcome Data

Hemoglobin Levels

Initial data analysis focused on comparison of Hgb means between the control and protocol group Group statistics demonstrated that the means between the groups were

similar (Figure 10) The largest difference of means was 4 g/L Data from more than 14 protocol group patients was missing for the months of December, March and July The control group had much less missing data with an average of 3 cases per month and a maximum of 6 cases missing in August The protocol group number of patients ranges from 21-43 and the control group number ranges from 58-61

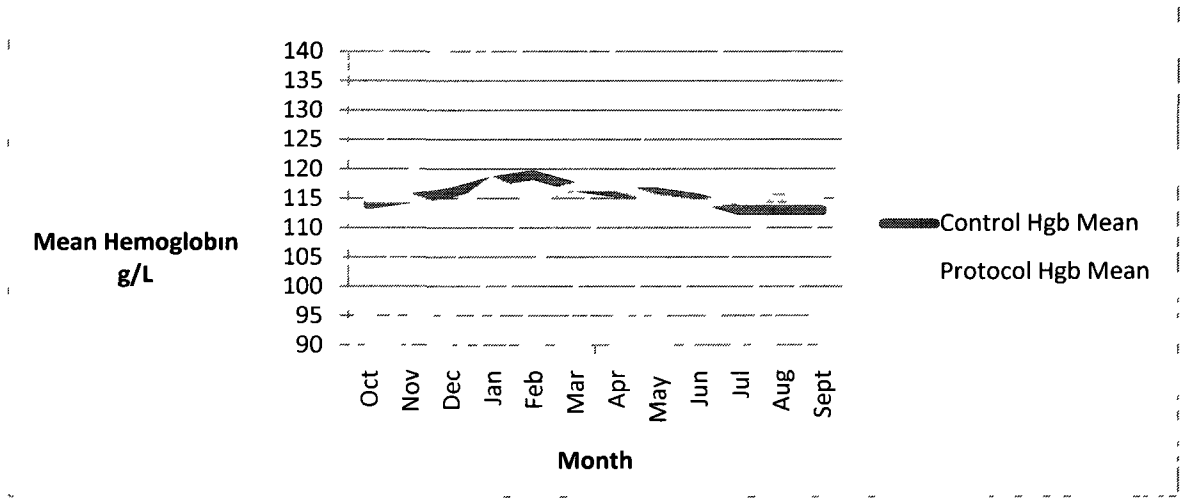

Figure 10 A comparison of hemoglobin level means between the control and protocol groups

An independent, non directional, *t*–test was performed to compare differences of mean Hgb levels between the protocol group and control group A Levene's test for equality of variances indicated a $p > 05$ value for each month, suggesting that the variability in the groups was consistent and therefore equal variances was assumed in all cases (Appendix F) Calculation of Cohen's *d* effect size indicated that every month had trivial or small, effect size results (Appendix F) For purposes of this study, trivial effect size in a two-group test of mean differences was defined as <0 20, a small effect size was between 0 20 and 0 49, a medium effect size was between 0 50 and 0 79, and a large effect size was 0 80 or greater (Cohen, 1988) The *t*-test for equality of means indicated a $p > 05$ for every month, and in

addition to effect sizes, no significant statistical differences in Hgb means were identified between the groups (Appendix D)

Following the *t*-test, Hgb data were regrouped into three categories below target, 75-109g/L, target, 110-125 g/L, above target, 126-145 g/L These categories were based on Hgb values that indicate below target, target and above target according to KDOQI guidelines used to develop the renal anemia management protocol (Appendix G) To determine whether the Hgb categorical outcomes of the groups were statistically different, a chi square test of independence was conducted In every category, the observed and expected values were similar The p values were > 05 every month indicating both groups were not statistically different from each other For every month there was no indication that the ratios of below target, target or above target differed between the protocol and control groups

Although categorizing the data into above or below targets (110-125 g/L) was used in the previous testing, neither category could be considered more unsafe for the patient than the other Categorizing the data into two categories to indicate *on* or *off* target was useful for further testing to determine if there were differences in the control and protocol group Hgb means The on target category was defined as Hgb values of 110-125 g/L, while off target category was defined as all Hgb values outside the target category range To determine if the Hgb observed values of the groups were statistically different, chi square testing was performed For all months there was no evidence of statistically significant differences between the groups, with on target or off target values p > 05 in all cases (Appendix H) Because of the consistent chi-square statistics indicating the control and protocol groups were not statistically different from each other, no significant differences were found between the groups based on categorical comparison of on and off target Hgb

To improve sensitivity of the testing, a repeated measures test under the General Linear Model was attempted There were limited number of protocol patients with consecutive monthly Hgb levels present in the database (n=8) therefore conducting a repeated measures statistical test was not practical

Transferrin Saturation Levels

Transferrin saturation results were reviewed to determine if there were differences between the groups Transferrin saturation (TSAT) levels have a direct impact on the efficacy of erythropoietin stimulating agents as well as being a key indicator to assess iron needs (Kalantar-Zadeh et al , 1998, Pisoni et al , 2004) The protocol group using RAMP had TSAT levels drawn every three months routinely, periodic levels drawn dependent on the TSAT level, and follow up levels drawn after the use of intravenous iron The control group had monthly TSAT levels drawn The number of patients with TSAT levels differs considerably each month, particularly in the protocol group (Tables 8 and 9)

Table 8
Control Group Mean Transferrin Saturation Levels and z Scores

Month	*N*	Target Mean	Control Mean	SD	*z*-Score	% Patients ≥ 0 2
October	61	≥0 2	0 13	0 07	1 02	15
November	59	≥0 2	0 13	0 06	1 10	14
December	61	≥0 2	0 16	0 07	0 59	28
January	60	≥0 2	0 16	0 06	0 72	24
February	60	≥0 2	0 16	0 06	0 72	24
March	60	≥0 2	0 15	0 07	0 75	23
April	61	≥0 2	0 17	0 10	0 27	39
May	59	≥0 2	0 16	0 07	0 58	28
June	60	≥0 2	0 17	0 07	0 47	32
July	61	≥0 2	0 15	0 06	0 74	22
August	55	≥0 2	0 15	0 06	0 82	21
September	60	≥0 2	0 17	0 07	0 53	30

To compare the TSAT means of the control and protocol groups, each mean was compared to the number of standard deviations above or below the target, using the KDOQI

guidelines value of TSAT ≥0 2 as the target mean Each *z*-score was calculated based on the number of standard deviations from the target The control group *z*-scores were consistently above zero while the protocol group *z*-scores were below zero The *z*-score was converted to a percentage based on assumed normality of distribution The percentage of patients reaching the target TSAT levels are presented in Table 8 and 9

Table 9
Protocol Group Mean Transferrin Saturation Levels and z-Scores

Month	*n*	Target Mean	Protocol Mean	SD	*z*-Score	% Patients ≥ 0 2
October	8	≥0 2	0 34	0 17	-0 86	81
November	39	≥0 2	0 28	0 11	-0 73	77
December	9	≥0 2	0 35	0 21	-0 72	76
January	32	≥0 2	0 27	0 08	-0 87	81
February	34	≥0 2	0 31	0 10	-1 10	86
March	14	≥0 2	0 32	0 19	-0 62	73
April	14	≥0 2	0 35	0 15	-1 00	84
May	36	≥0 2	0 28	0 12	-0 65	74
June	9	≥0 2	0 30	0 22	-0 47	68
July	13	≥0 2	0 28	0 09	-0 91	82
August	27	≥0 2	0 31	0 12	-0 85	80
September	14	≥0 2	0 30	0 14	-0 69	75

The percentages of patients reaching targets indicate that the control group had TSAT means that were consistently below acceptable targets (Figure 11) The control group had an interquartile range of 22-28% of patients reaching target mean TSAT levels while the protocol group had an interquartile range of 75-81 % of patients reaching those levels With less serum iron saturation testing and the use of the RAMP, the protocol group had reached acceptable TSAT levels

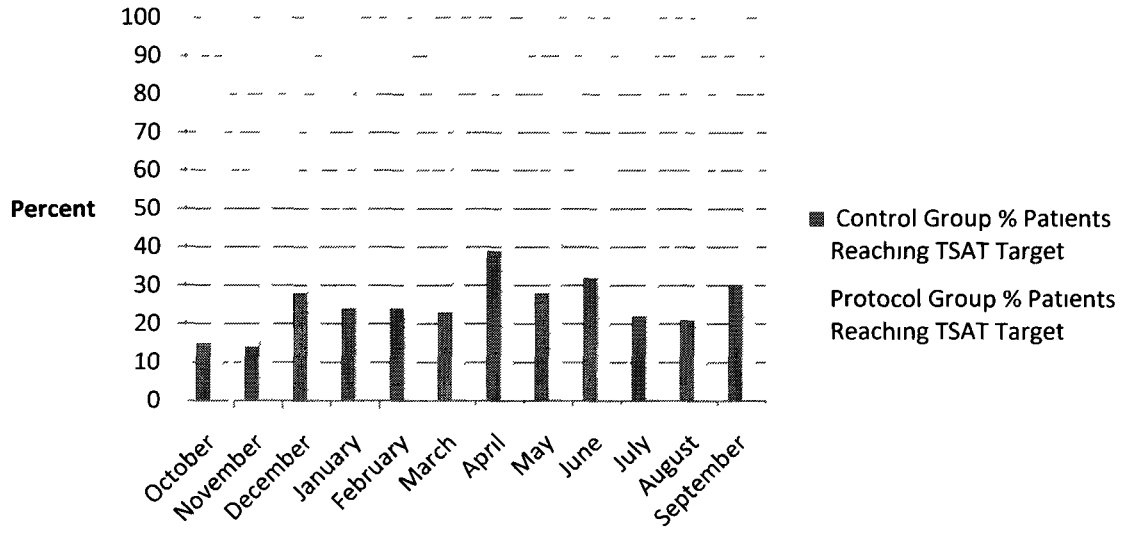

Figure 11 The percentage of patients reaching target transferrin saturation levels in the control and protocol groups

Ferritin Levels

Ferritin is a protein that stores iron that is released and transported to necessary areas in the body Ferritin levels were not consistently available on a monthly basis in the control group The protocol group had ferritin levels drawn based on the RAMP recommendations The ferritin monthly mean levels are shown in Figure 12 KDOQI guidelines recommend maintaining ferritin levels at 200-500 µg/ml during ESA treatment to avoid iron deficiency in hemodialysis patients (National Kidney Foundation, 2006) The protocol group had monthly mean ferritin levels above 600 ug/L throughout the study No ferritin levels were available in the control group in May and August Control group monthly mean levels were below 500 µg/L in each month except November Data on ferritin levels were low for patients in the protocol group and not consistently available for patients in the control group, and therefore statistical testing to compare the means was not feasible

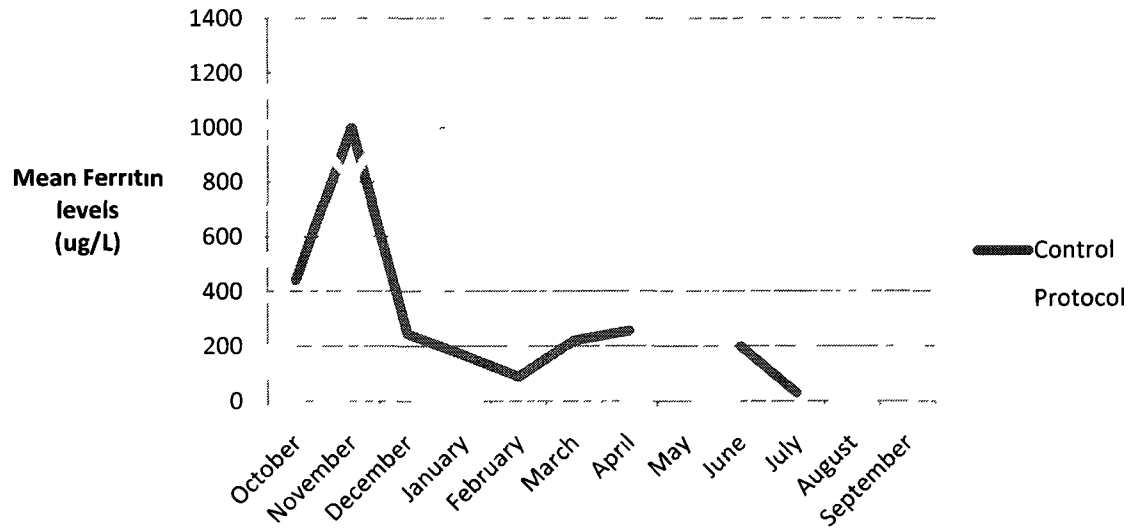

Figure 12 Monthly mean ferritin levels (ug/L) in the control and protocol groups

Analysis of Renal Anemia Medication Use

Intravenous Iron

A comparison of the use of intravenous iron between the control and protocol groups required an examination of the elemental iron in each medication The control group used intravenous iron saccharate while the protocol group used intravenous iron gluconate and iron dextran Although different iron preparations are used, each dose refers to the amount of elemental iron in the dose

In both groups, the number of patients that used intravenous iron at any point in the study was inconsistent Patients were given intravenous iron based on need At any given point in the study, there were 10-17 control group patients and 13-22 protocol group patients using intravenous iron Mean dosages were used to determine the monthly use of intravenous elemental iron in each group, and comparisons of total mean group dosages of the control and protocol groups were performed

The trend in iron use for both groups differs throughout the study The protocol group used less intravenous iron than the control group in every month with the exception of October, November and August (Figure 13) The control group required approximately 9,500 mg more of intravenous iron over the course of the study when compared to the protocol group

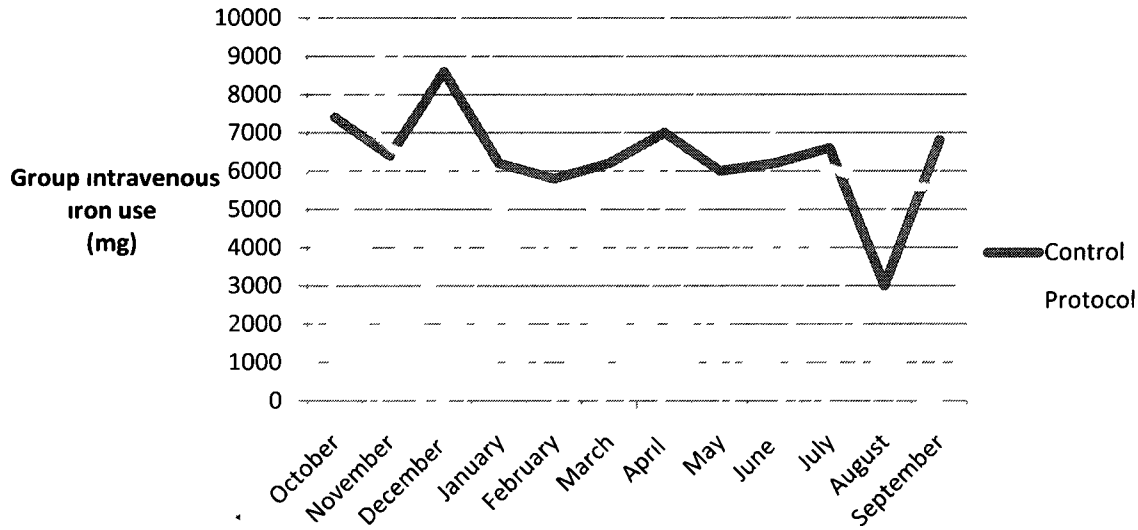

Figure 13 Total group monthly intravenous iron use in control and protocol groups

Erythropoietin Stimulating Agents

Erythropoietin stimulating agents were divided into two categories Darbepoetin and epoetin alfa are the two preparations of the drug used in this study Due to low numbers of patients using darbepoetin (n= 2-6), an analysis of effect size was conducted to determine the chance of Type II error Table 10 highlights the mean difference and effect size of the relationship between the mean dosages of both groups The standard deviation of the control group was used in the calculations since this is the group for which effectiveness of the protocol was being compared Seven out of twelve months had medium effect sizes, four had large effect sizes and one had small effect sizes A t-test indicated there were no significant differences (p> 05) in mean values between the control and protocol groups in the

darbepoetin dosage category This is likely a type II error because the *t*-test could not detect significant differences, despite the evidence of medium effect sizes in seven out of twelve months The *t*-test is lacking sensitivity due to small sample sizes

Table 10
Effect Size of the Difference Between the Means of Control and Protocol Darbepoetin Alfa Dosages

Month	Mean difference	SD	Cohen's *d*	Effect Size
October	-89 07	131 70	0 67	Medium
November	-101 32	139 36	0 72	Medium
December	-115 82	139 36	0 83	Large
January	-130 28	135 70	0 96	Large
February	-79 60	156 56	0 51	Medium
March	-79 60	156 56	0 51	Medium
April	-50 65	149 58	0 33	Small
May	-123 05	149 58	0 82	Large
June	-101 32	149 58	0 68	Medium
July	-86 85	145 32	0 60	Medium
August	-86 85	145 32	0 60	Medium
September	-115 82	145 32	0 80	Large

Note $p > 05$ *for all months analyzed*

A majority of patients in both groups were using epoetin alfa as an erythropoietin stimulating agent Equal variances were assumed in all months with the exception of April, May and June (Appendix I) Effect sizes for 9 out of 12 months demonstrated small effect sizes (Appendix I) An independent, non directional *t*-test was performed to determine if there were differences between the means of epoetin alfa dosages in the control and protocol dosages For each month, there were no significant differences ($p > 05$) between the mean dosages of epoetin alfa of the control and protocol groups (Table 11)

Table 11

The t-tests for the Equality of Means in Epoetin Alfa Dosages Between the Control and Protocol Groups

Month	Equal variances	*t*	*df*	*p*
October mean epoetin alfa dose	assumed	0 153	93	88
November mean epoetin alfa dose	assumed	0 082	90	93
December mean epoetin alfa dose	assumed	0 197	90	84
January mean epoetin alfa dose	assumed	-0 159	91	87
February mean epoetin alfa dose	assumed	-0 497	88	62
March mean epoetin alfa dose	assumed	-0 719	88	47
April mean epoetin alfa dose	not assumed	-1 209	59	27
May mean epoetin alfa dose	not assumed	-1 214	57	27
June mean epoetin alfa dose	not assumed	-1 176	53	25
July mean epoetin alfa dose	assumed	-1 243	90	22
August mean epoetin alfa dose	assumed	-1 215	90	23
September mean epoetin alfa dose	assumed	-1 113	89	27

To examine the average use of epoetin alfa per person in the control (n=55) and protocol (n=37) groups, the sum of the mean averages were divided by the number of patients using epoetin alfa in the group Figure 14 indicates that the average use at the beginning of the study was very similar for the control and protocol group at approximately 48,000 and 50,000 units per person respectively The use of epoetin alfa in the control group decreased progressively by approximately 3,000 units in May and then trended to levels similar to October results by the end of the study The use of epoetin alfa in the protocol group trended upwards by almost 10,000 units per person, per month by the end of the study

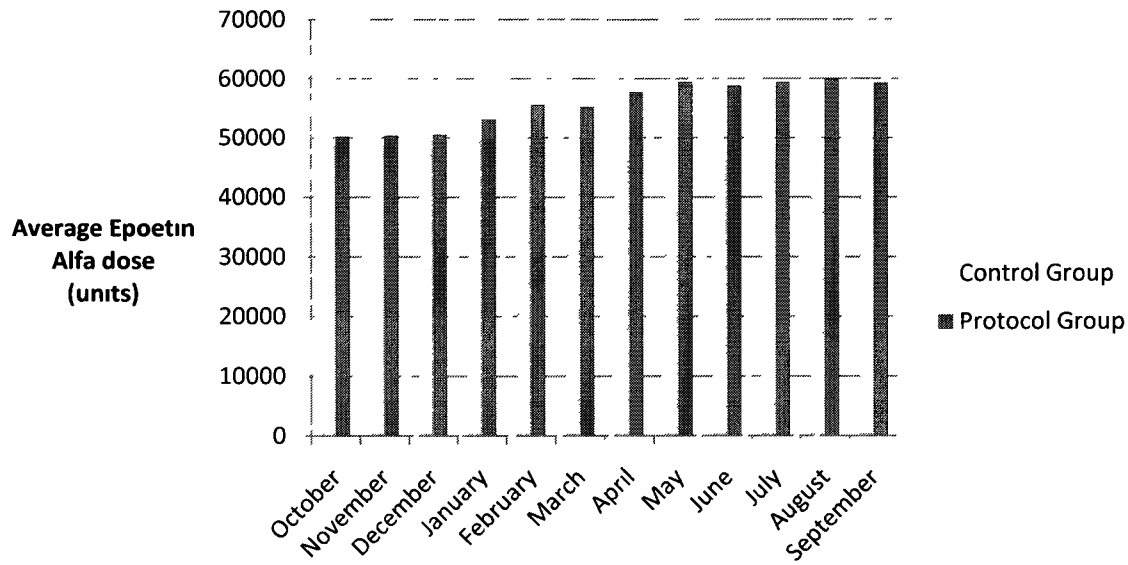

Figure 14 The average dose of epoetin alfa per person in the control and protocol groups

Confounding Variables

To examine the effect any extraneous variables may have on the ESA dosages between the groups, *t*-tests were performed to determine if there were statistically significant differences between potential confounding variables There were noticeable differences in gender, race and co-morbidity frequency in the groups Further non directional *t*-tests show that there were significant differences ($p< 05$) between the incidence of diabetes, cerebrovascular accidents, congestive heart failure, myocardial infarction and hypertension between the control and protocol groups There were no significant differences of dyslipidemia incidence means between the control and protocol groups

An examination of the entire group of patients was performed to determine if there were differences in race and co-morbidities The groups were tested together due to the low numbers of First Nations patients in the control group There were no significant differences ($p> 05$) in the total group of patients (both control and protocol combined) between Caucasian and First Nations means for all co-morbidity incidence

Next, a *t*-test to show if there were any significant gender differences in the control and protocol groups for use of Epoetin Alfa was completed Results indicated $p > 05$ for every month, therefore no significant differences were detected A *t*-test to determine if there were significant differences in each group between Caucasians and First Nations use of Epoetin Alfa was performed thereafter There were no significant differences between these races and Epoetin Alfa dosages in all the months in the control group and 10 out of 12 of the months in the protocol group ($p > 05$)

An attempt to find significant differences between the iron dosages and co-morbidity incidence was not feasible due to low numbers of patients using each preparation of intravenous iron in each group The tables for each of these *t*-tests were not included in this study

Economic Analysis

An analysis of the cost effectiveness of the protocol was assessed, by examining the costs of intravenous iron and epoetin alfa treatments A comparison of the control and protocol group provided information regarding the cost of a non-protocol and protocol approach to renal anemia management All costs for medications are based on BCPRA 2009 summary of monthly drug costs (British Columbia Provincial Renal Agency, 2009b)

Intravenous Iron

When comparing monthly expenses for intravenous iron, the control group had elevated costs related to higher use of iron and the type of iron used The cost of iron saccharate is $36 63/100 mg, iron dextran is $16 83/100 mg and iron gluconate is $19 96/100 mg (British Columbia Provincial Renal Agency, 2009b) Over the time period of the study, the total intravenous iron cost of the control group was approximately $17,000 more than the protocol group (Fig 15)

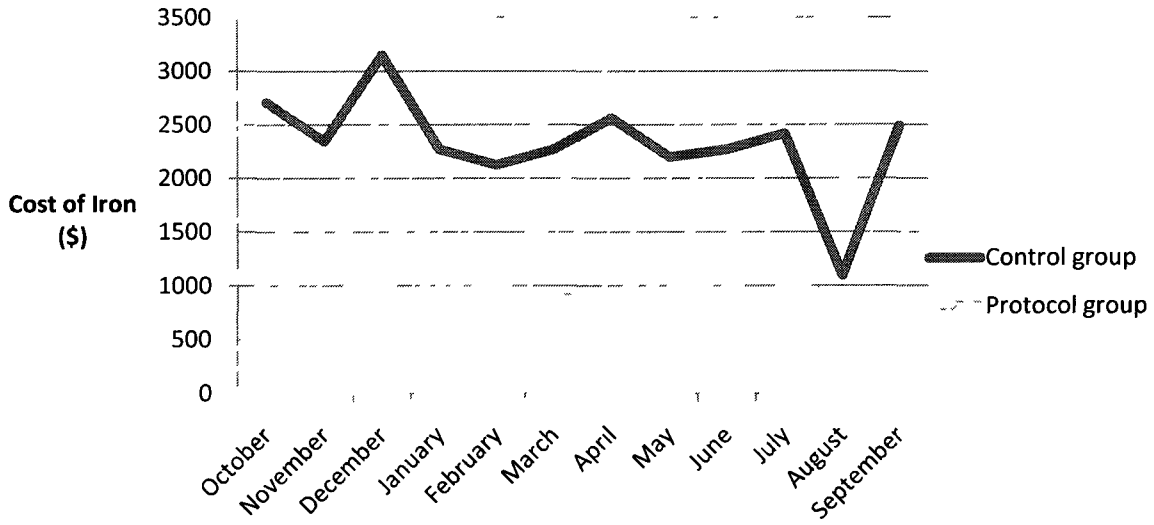

Figure 15 Total monthly cost of intravenous iron in control and protocol groups

Epoetin Alfa

An analysis of the cost of epoetin alfa treatment in the control and protocol group is presented in Table 12 The cost of epoetin alfa is $17 11 per 200 units (British Columbia Provincial Renal Agency, 2009b) Although both groups began with similar costs, the protocol group had significant cost increases during the study By completion of the study the costs were almost $950 dollars more per month per person in the protocol group The overall cost difference per person during the study is $8,135 more in the protocol group

Table 12

Average per Patient Cost for Epoetin Alfa in the Control and Protocol Groups

Month	Group	Avg Dosage per Patient	Cost per Month ($)
October	Control	48640	4159
	Protocol	50261	4297
November	Control	48785	4171
	Protocol	50377	4307
December	Control	49799	4258
	Protocol	50594	4326
January	Control	49711	4250
	Protocol	53173	4546
February	Control	48770	4169
	Protocol	55567	4751
March	Control	46840	4005
	Protocol	55232	4722
April	Control	46189	3949
	Protocol	57760	4938
May	Control	45899	3924
	Protocol	59429	5081
June	Control	46189	3949
	Protocol	58857	5032
July	Control	46912	4011
	Protocol	59389	5078
August	Control	47709	4079
	Protocol	60040	5133
September	Control	48142	4116
	Protocol	59352	5074

CHAPTER 5

Discussion

In this case-control study, a group of hemodialysis patients using a RAMP was compared to a control group of hemodialysis patients for whom a protocol was not utilized The groups were comparable in age, time on hemodialysis and number of days without hospitalization

Research Question One

In the hemodialysis population, does using a nurse-driven RAMP enable patients to maintain target Hgb levels as effectively as a non-protocol based physician-driven approach? When examining the Hgb level means throughout the study, the control and protocol groups maintained target Hgb levels Using *t*-tests, there were no significant differences ($p > 05$) in the Hgb levels between the groups In addition, when the groups were separated into below and above target categories, there were no significant differences between the protocol and control groups In this study, hemodialysis patients in the protocol group maintained Hgb target levels as effectively as hemodialysis patients in the control group These findings provide some evidence to indicate that the use of nurse-driven anemia protocols can contribute to safe patient outcomes in the hemodialysis setting, as it pertains to maintaining target hemoglobin levels

Research Question Two

Is there a relationship between an anemia management practice approach and Hgb levels, iron levels, intravenous iron use, and erythropoietin use in the hemodialysis setting? Throughout the study, iron saturation levels tended to reach target levels for the protocol group The measure of iron saturation levels available for red blood cell production is not a direct indicator of effective anemia control but evidence shows a strong association between

transferrin saturation (TSAT) levels and anemia control (Pisoni et al, 2004) KDOQI guidelines recommend TSAT levels > 0 20 to prevent iron deficiency anemia (National Kidney Foundation, 2006) For the protocol group, approximately 78% of their patients reached TSAT levels of 20, while approximately 25% of the control group reached that level The RAMP has specific interventions targeted at treating low TSAT levels

The low rates of acceptable TSAT levels in the control group did not appear to affect the achievement of target Hgb levels Nothing in literature reviewed for this study addressed the impact of low TSAT on target Hgb, with the exception that TSAT levels do not have a direct cause and effect relationship with hemoglobin level, they are only associated between the variables Further studies examining TSAT levels and their relationship with target Hgb levels in hemodialysis patients are required to determine acceptable TSAT levels for renal anemia management

The control group had monthly TSAT levels drawn, which reflected intensive monitoring, but did not appear to contribute to better health outcomes The TSAT levels remained far below target levels throughout the study The protocol group was tested for TSAT levels every three months and randomly depending on intravenous iron use Although the protocol group was tested less frequently, the patient outcomes were much better, with the added benefit of less discomfort to the patient and greater cost savings The cost of serum TSAT testing is $19 86 (A Arsenault, economics assistant, BCMA, personal communication, April 27, 2010) Monthly TSAT testing appears to be a costly and unnecessary intervention for patients

Ferritin levels differed noticeably between the control and protocol groups Ferritin levels should be maintained at 200-500 ug/L to prevent iron deficiency in hemodialysis patients treated with an ESA (National Kidney Foundation, 2006) In this study, the control

group had ferritin levels consistently below 250 ug/L with the exception of two months where data was unavailable In spite of these two absent data points, the average ferritin level for the duration of the study was close to 300 ug/L Unfortunately there was sporadic data available in the control group due to testing based on individual needs and not as a scheduled unit routine As a result, statistical testing was not feasible This finding speaks to the need to monitor ferritin levels in practice, based on a more standardized protocol such as the RAMP utilized in this study

The protocol group had monthly ferritin levels greater than 600 ug/L The average ferritin level for the protocol group was close to 800 ug/L Evidence shows that hemodialysis patients often have elevated ferritin levels related to inflammation, which interferes with the synthesis and clearance of ferritin (Easom, 2006) Elevated ferritin levels pose a problem when using stringent protocol guidelines The RAMP uses ferritin levels of >500 ug/L as an indication of iron overload although in the protocol group, this may be associated with underlying inflammation related to cardiac co-morbidities in the patients Further research is recommended to determine if there are statistically significant differences in ferritin levels between the groups and the implications that these differences may have for anemia management As well, further investigation into validity of using ferritin as an iron status indicator in the hemodialysis population is suggested

The use of intravenous iron was also an indicator of anemia management that differed between the groups Although different intravenous iron preparations were used in each group, a comparison of elemental iron in each preparation allowed a comparison of iron use Iron doses were greater in the control group resulting in an overall use that was nearly 10 g more than the protocol group The higher iron doses in the control group were inconsistent with the low TSAT levels Results from this study suggest that iron deficiency was present

in the control group despite treatment with intravenous iron Low transferrin saturation despite treatment indicates a need to further investigate the relationship between transferrin saturation and iron deficiency and its impact on anemia management in hemodialysis patients

When examining the repercussions of using intravenous iron at higher rates, most health care institutions focus on costs The costs of intravenous iron are substantial, depending on the type of iron in use The cost of iron saccharate ($36 63/100mg) is much higher than iron gluconate ($19 96/100mg) and iron dextran ($16 83/100mg) (British Columbia Provincial Renal Agency, 2009b) The control group used iron saccharate exclusively, contributing to the inflated costs of iron treatment in comparison to the protocol group, which used iron gluconate and iron dextran The overall protocol group intravenous iron cost over the 12 month study period was $17000 less than the overall control group cost These are significant cost savings that could be related the type of iron used, in addition to the use of a protocol that facilitated the appropriate treatment of iron deficiency

Another variable which showed differences between groups was the overall use of erythropoietin stimulating agents Although there was no statistically significant differences ($p > 05$) between the means of epoetin alfa dosages of each group, the average dose per person showed trends that indicate slightly greater use in the protocol group In the last 8 months of the study, the protocol group displayed an increased use of nearly 10000 units per person compared to the control group The protocol group had over $8000 higher costs per person for the use of epoetin alfa compared to the control group during the study The high cost of this medication and the trend of increased use of epoetin alfa present a concern about the financial implications of standardized dosing in a RAMP such as the one used for this study

The increased use of epoetin alfa in the protocol group is an indication of hyporesponse to the drug and hyporesponse was considered a confounding variable in this study Evidence demonstrates that hyporesponse to ESAs are associated with inflammation The higher incidence of cardiovascular co-morbidities in the protocol group could also provide an explanation for hyporesponse to epoetin alfa The influence of prevalence of cardiac co-morbidities was not considered a confounding variable at the study design stage Furthermore, the higher incidence of diabetes in the protocol group and the ensuing inflammatory process related to infection, microvascular disease, and atherosclerosis could play a role in hyporesponse to epoetin alfa

Hyporesponse to epoetin alfa in conjunction with higher ferritin levels in the protocol group suggests the need for further investigation to determine if the protocol group had a higher incidence of inflammatory disorders or processes as compared to the control group Further need for prospective trials to examine the relationship between the presence of cardiac comorbidities in hemodialysis patients and response to ESA's are also indicated

Another potential confounding variable is the higher First Nations population in the protocol group Although this study attempted to explore a relationship between ethnicity and ESA response through correlational analysis, limited numbers of patients from First Nations background in the control group prevented this Future research is warranted to examine if there is a relationship between First Nations ethnicity and ESA response

The higher population of First Nations people in Northern British Columbia is a predictable finding from this study The challenges that the Northern Renal program faces is unique in the province Northern British Columbia has nearly 16% of its population identified as aboriginal located at 80 reserve First Nations communities (BC Stats, 2007a, Tabobondung, 2007) The First Nations populations in Northern British Columbia are both

numerous and diverse compared to the rest of the province The overall prevalence of diabetes among First Nations populations in BC is at least 40% higher than that of the general BC population The prevalence of diabetic nephropathy is much higher in First Nations than in the general population, and the rates range from 25-60% following 15 to 20 years with diabetes (Whiteside, 1994) The risk of developing ESRD from diabetes in First Nations populations is three times higher than the general population and of those with ESRD, the relative risk of starting dialysis is 6 5 times higher than the general population (Young, Kaufert, McKenzie, Hawkins, & O'Neil, 1989) This finding indicates a need to account for the type of population that the NRP serves to assist in appropriate health service planning, funding and policy development in this region

This study explored patient structural variables and the independent or dependent role of the nurse resulting in nurse sensitive outcomes As indicated previously, the patient variables, such as co-morbidities, may have a significant influence on the patient outcomes of ESA use There is no conclusive evidence to indicate that higher ESA use in the protocol group is directly related to the independent role of the nurse in renal anemia management The higher ESA use may be related to deficiencies in the protocol in regards to dosing for patients with cardiac co-morbidities In contrast, the patient outcome of increased use of intravenous iron could be related to the dependent role of the nurse and lack of decision-making tools to properly treat iron deficiency The complexity of the interrelationship between patient outcomes such as Hgb, ferritin, TSAT, iron and ESA use, as well as patient variables such as diagnosis, race and the presence of co-morbidities complicates evaluating the process variables of the independent and dependent roles of the nurses In spite of challenges of examining the roles of nurses in this study, the protocol nurses are primarily responsible for ensuring that patients reach target Hgb levels Due to iron levels outside of

the parameter of the RAMP, in this case higher ferritin levels in the protocol group, physician or pharmacist consultation was required

The NREM provided a framework to determine how nurse-driven anemia management contributes to nurse sensitive patient outcomes It was useful to conceptualize renal anemia management through a structure, process and outcome model that specifically examines the impact that nursing actions have on patient outcomes The structural component was applicable to this study by focusing on the patient variables which can impact patient outcomes In this study, patient co-morbidities and ethnicity had the potential of influencing patient outcomes This study did not examine nursing or organizational structural components as outlined by the NREM The influence of individual nursing variables such as education and experience, as well as organizational variables of staffing or hospital policy on patient outcomes in this study are unknown at this time Nursing research to test the NREM in the hemodialysis setting, to further explore nursing and organizational variables and their impact on patient outcomes is suggested

Examining the process component by delineating the roles that nurses acquire to provide renal anemia management to the hemodialysis patient indicated that the control group maintained a dependent role while the protocol group used a combination of independent and interdependent roles The NREM also showed the relationship between the structure and process and its impact on outcomes In this study, physiological patient biomarkers such as Hgb were identified as potential nurse sensitive outcomes, directly influenced by nursing roles and patient variables Examining nurse sensitive outcomes in the hemodialysis setting informs the health care system of the contributions of nephrology nursing practice

In this study, the protocol nurses were the renal care professionals that provided most of the treatment care for the RAMP resulting in physiological patient outcomes The activities associated with the independent role of the nurse included assessment of lab work, assessment of patient's condition, decision-making regarding a plan of care and intervention according to protocol guidelines Therefore, using a nurse-driven RAMP in hemodialysis patients may have resulted in Hgb levels identified as a clinical nurse sensitive patient outcome

CHAPTER 6

Conclusion

This study examined patient outcomes pertaining to the use of a RAMP to care for hemodialysis patients The study provided some evidence that the use of a nurse-driven protocol is as effective as a non-protocol, physician-based practice approach to renal anemia management Each group reached and maintained acceptable target Hgb ranges during the course of the study The study also demonstrated that the relationship between the practice approach to anemia management and Hgb levels, iron levels, intravenous iron use and ESA use cannot be evaluated effectively based on the complexity of the interrelationship between the variables

Nurses at the NRP were meeting nephrology nursing standards by utilizing a RAMP The change in decision-making structure had enabled nurses to work to a full scope of practice in managing renal anemia by increasing their responsibilities in the process of assessment, planning and evaluation of hemodialysis patients Through the use of a decision support tool, namely the RAMP, nurses at the NRP were maintaining acceptable target Hgb levels in their hemodialysis patients

Although this tool enabled nurses to provide the necessary actions to maintain Hgb levels, evidence from this study also indicated a need to examine the use and dosing of intravenous iron preparations and their relationship to iron level indicators in addition to ESA dosing and its impact on Hgb levels The relationship between these indicators was found to be more complex than anticipated at the study outset A link between these indicators was assumed but results from this study demonstrated otherwise For example, the literature provided a strong association between adequate TSAT levels and target Hgb levels although results from the control group in this study demonstrated otherwise Also, the influence of

confounding variables such as race, diagnosis and co-morbidity incidence may have added to the complexity of examining target Hgb levels in the hemodialysis population

The higher incidence of cardiac co-morbidities and diabetes in the hemodialysis patients treated by the NRP challenges the idea that a standardized protocol fits all patients Inflammatory processes related to cardiac co-morbidities or diabetes could play a role in the clinical effectiveness and financial efficacy of anemia management protocols The incidence of erythropoietin hyporesponse coupled with higher ferritin levels creates new issues of financial feasibility for components of this protocol, particularly standardized dosing for all patients Prospective trials investigating alternate dosing patterns based on the incidence of inflammatory conditions are needed to provide evidence that will direct decisions about the use of ESA's

This study examined how nurse-driven approach compares to physician-driven practice approach to renal anemia management Evaluation of nurse-driven protocols is necessary to determine how the role of the nurse evolves with practice changes and the resulting impact on patient care outcomes Using the NREM, the changes in the role of the nurse were delineated in each approach to determine if nurse sensitive patient outcomes could be identified in the protocol approach This study demonstrated that Hgb levels may be attributed to the independent role of nursing and be identified as a nurse sensitive patient outcome in nurse-driven renal anemia management

Anemia management protocols are commonly being used in the hemodialysis setting to provide efficient, cost effective renal care Results from this study suggest that using a protocol directs nurses in providing renal anemia management in an efficient manner, potentially reducing the need for frequent lab testing and nephrologist consultation Cost effectiveness of aspects of the nurse-driven protocol was questionable Although iron doses

were lower and also less costly than the control group, hyporesponse to the ESA could potentially be more expensive The use of a RAMP suggests that it is an effective tool with potentially higher costs The need to review ESA and iron dosing in the protocol as it relates to patient variables such as cardiac or other inflammatory processes is encouraged It is evident that more investigation is necessary to establish the relationship between iron and epoetin dosing and cost

A nursing limitation of this study is that the actions of the nurses were not directly measured to determine the time, education level, experience, and workload of each nurse and its influence on decision-making Although the use of the protocol was as effective as traditional physician practice, the impact on the nurses' workload and time management was not examined Further research is suggested to directly measure nursing experience, education and time as it relates to the use of the protocol and examine its connection with the nurse

There are three further limitations to this study First, only data available in the BCPRA PROMIS database was used As a result, data entry may be subject to error, omissions may be present and limited standard terminology of variable terms in the database all contribute to the quality of the data in this study Second, there were insufficient numbers of patients eligible to provide adequate power, particularly in the protocol group A post hoc power analysis of *t*-test difference between two independent means, n=106, p= 0 05 and effect size = 5 indicated a power of 71% was achieved Low patient numbers eliminated the possibility of matching subjects based gender, race and diagnosis They also reduced correlation testing possibilities, particularly when gender or race was posed as potential confounding variables Although higher sample sizes could have improved power in this study and reduced the risk of a Type II error, a false negative conclusion, the retrospective

nature of the study in two clinical settings with limited patient populations poses as an obstacle to increasing power of the study Third, medical practitioner preferences played a role in cost effectiveness Preference of type of intravenous iron ordered by physicians increased costs significantly for the control group

Identifying the most cost effective therapy for renal anemia in the hemodialysis setting without compromising efficacy or patient safety is an important objective for health care systems The health care system demands that programs demonstrate the impact nursing practice changes have on patient outcomes Nursing has a responsibility to ensure that their practices provide safe patient care in addition to meeting national standards Evaluating practice through patient outcomes achievement is one way to examine nursing practice

Evaluating patient outcomes in the health care system is an essential part of determining the impact of practice change The complexity of the hemodialysis patient contributes to the difficulty of examining renal anemia outcomes when implementing a protocol This study demonstrated that the use of a nurse-driven RAMP is as effective as a traditional physician approach in ensuring that target hemoglobin levels were reached The challenge is to look at the multifaceted issue of renal anemia and determine if these protocols require modification to better meet the needs of this patient population

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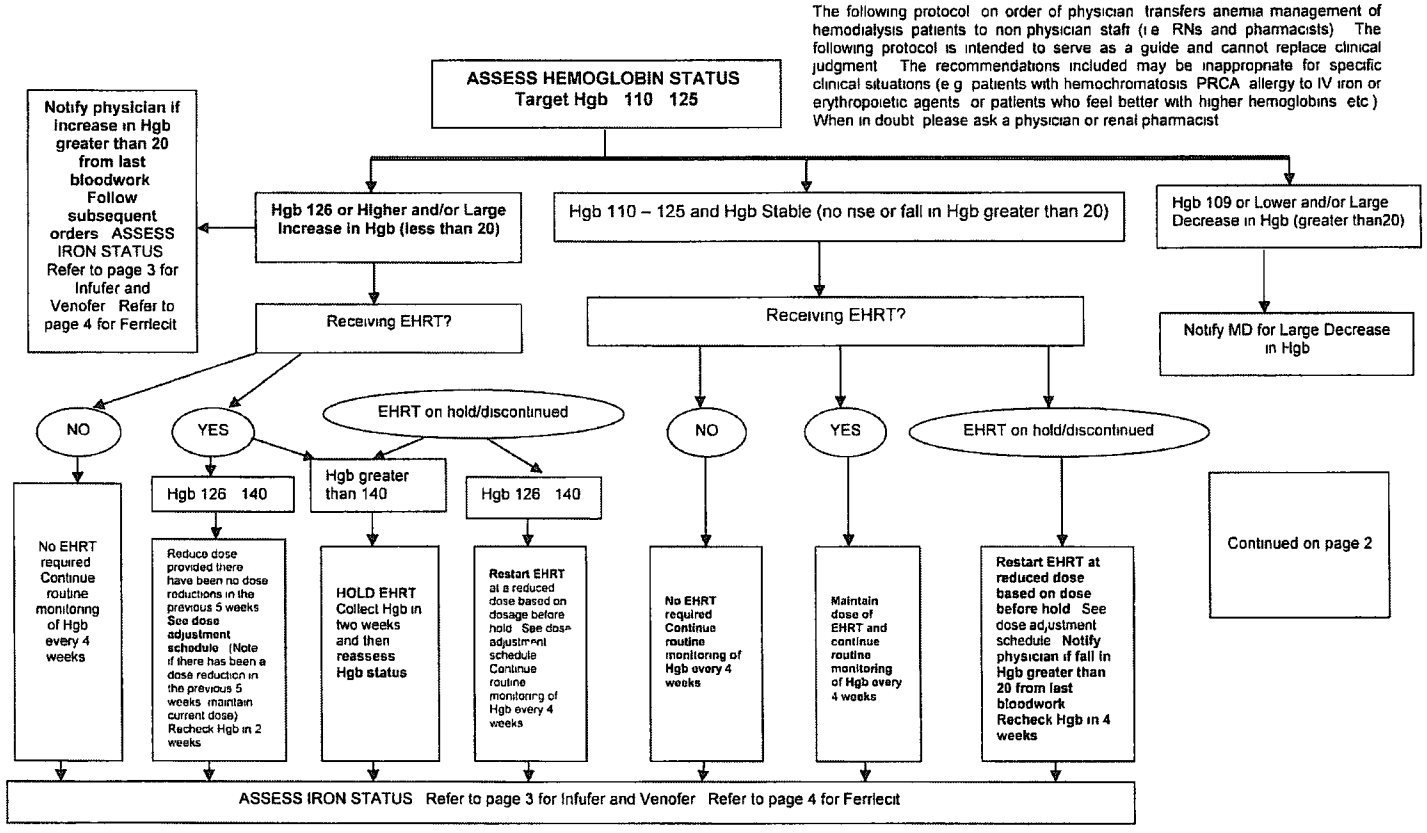
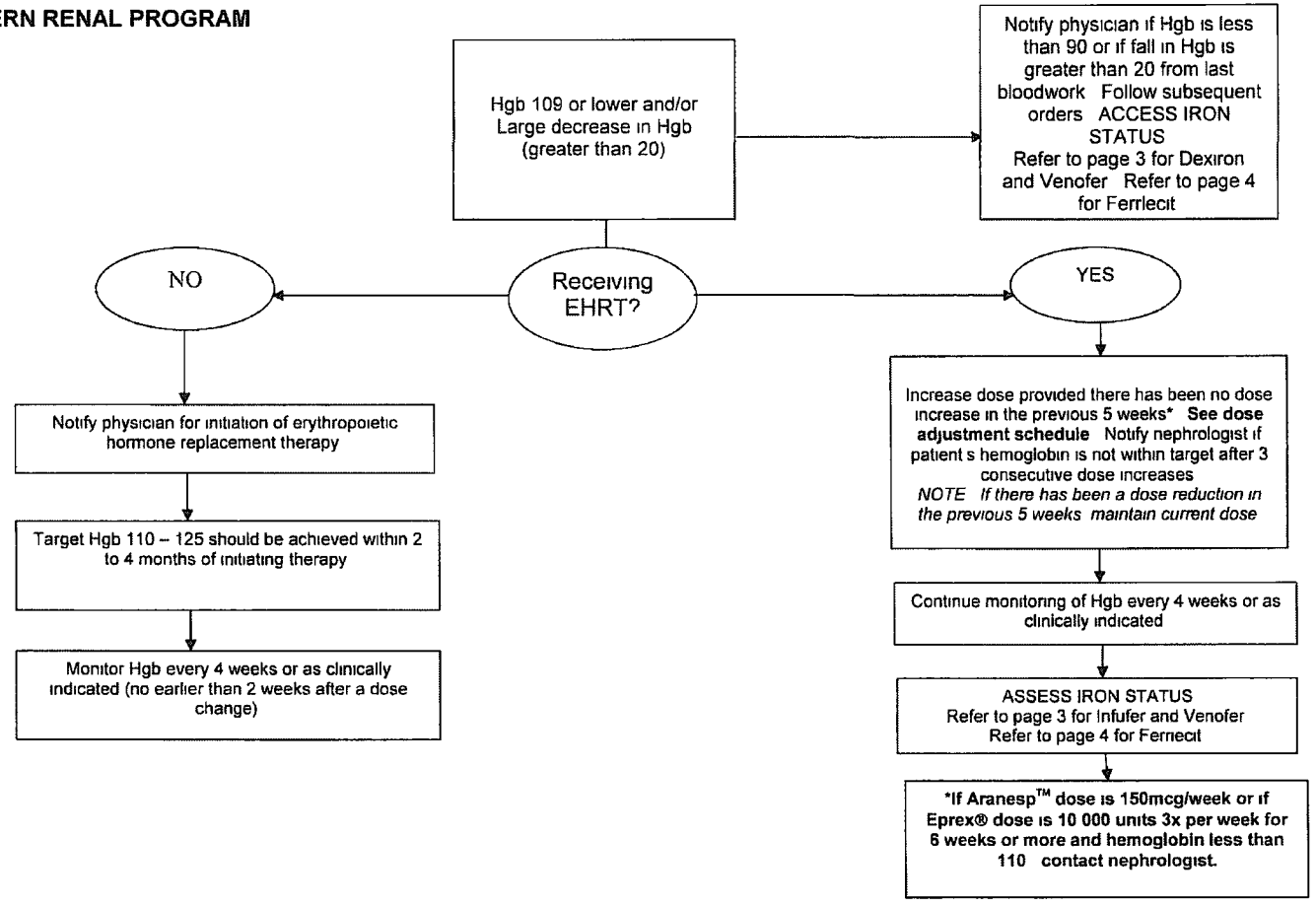
Appendix A
RENAL ANEMIA MANAGEMENT PROTOCOL

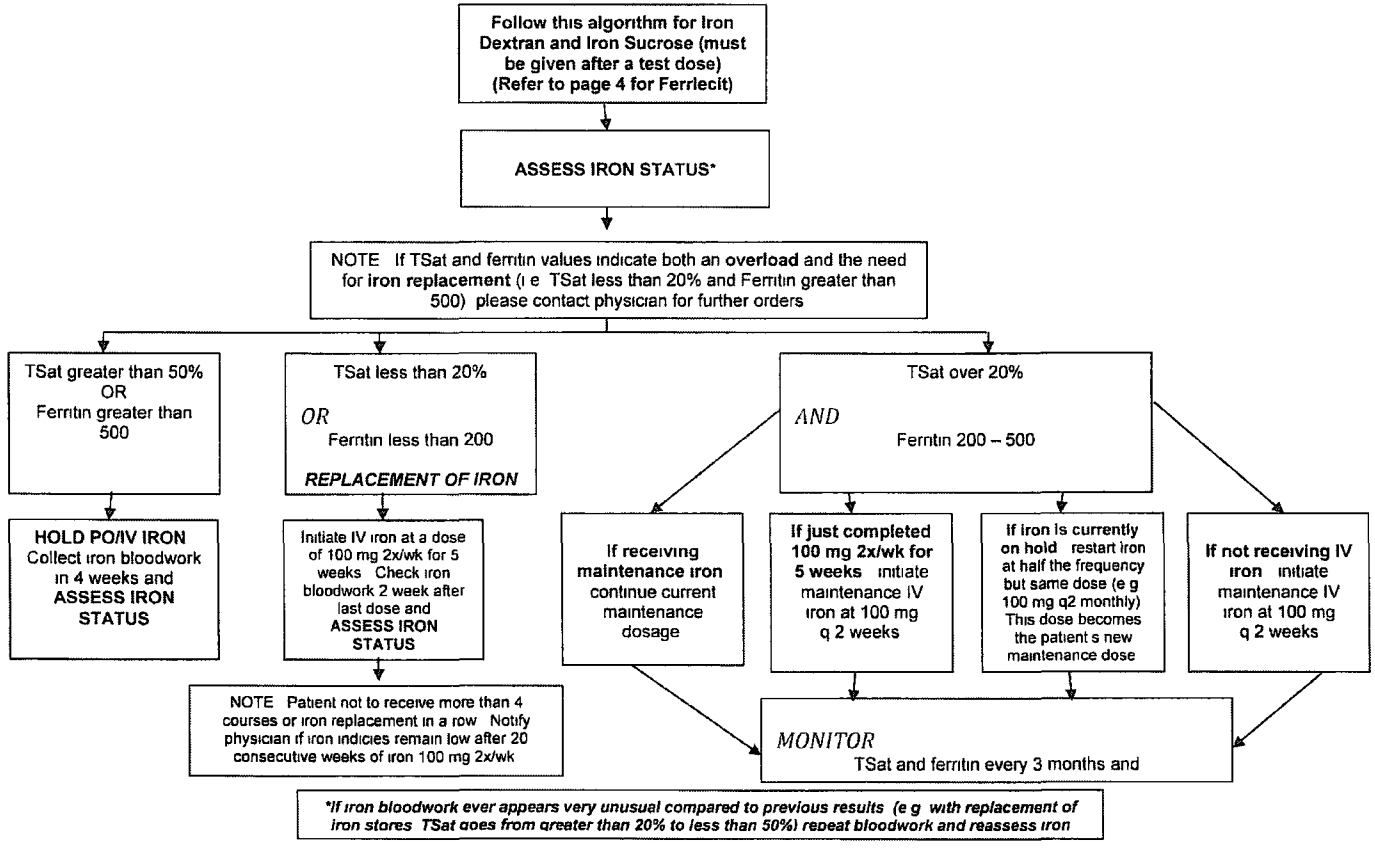
RP 010



NOTE Erythropoietic hormone replacement therapy (EHRT) refers to both Aranesp and Eprex

NORTHERN RENAL PROGRAM

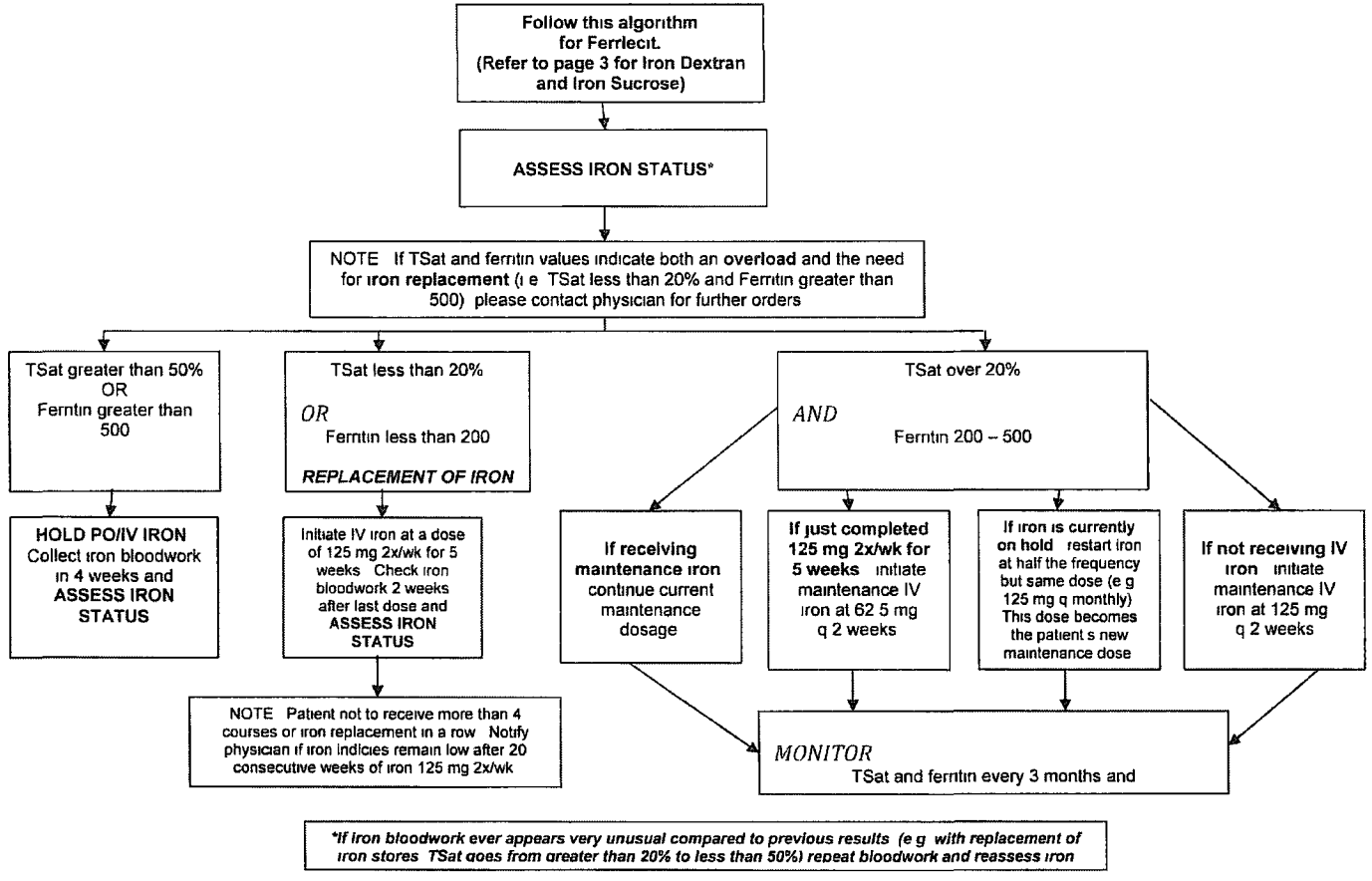




Note Iron maintenance dose refers to 100 q monthly unless otherwise indicated
Infufer refers to Iron Dextran

Venofer refers to Iron Sucrose

NORTHERN RENAL PROGRAM



If iron bloodwork ever appears very unusual compared to previous results (e g with replacement of iron stores TSat goes from greater than 20% to less than 50%) repeat bloodwork and reassess iron

Note Iron maintenance dose refers to 125 q monthly unless otherwise indicated

NORTHERN RENAL PROGRAM

DOSE ADJUSTMENT SCHEDULE FOR PATIENTS USING EPREX (ERYTHROPOIETIN)

The following chart provides the necessary changes for most dose increments or dose reductions If the patient's dosing does not fall into one of the intervals, contact the nephrologist

Eprex is available in multidose vials (20,000 units/mL)

- 2,000 units (0 1 mL)
- 3,000 units (0 15 mL)
- 4,000 units (0 2 mL)
- 5,000 units (0 25 mL)
- 6,000 units (0 3 mL)
- 8, 000 units (0 4 mL)
- 9,000 units (0 45 mL) and
- 10,000 units (0 5 mL)

Current Dose	**Increase Dose To**	**Reduce Dose To**
2,000 units/wk	3,000 units/wk	Discontinue Eprex
3,000 units/wk	4,000 units/wk	2,000 units/wk
4,000 units/wk	6,000 units/wk	3,000 units/wk
6,000 units/wk	4,000 units 2x/wk	4,000 units/wk
4,000 IU 2x/wk	5,000 IU 2x/wk	6,000 IU/wk
5,000 IU 2x/wk	6,000 IU 2x/wk	4 000 IU 2x/wk
6,000 IU 2x/wk	8,000 IU 2x/wk	5,000 IU 2x/wk
8,000 IU 2x/wk	9,000 IU 2x/wk	6,000 IU 2x/wk
9,000 IU 2x/wk	10,000 IU 2x/wk	8,000 IU 2x/wk
10,000 IU 2x/wk	8,000 IU 3x/wk	9,000 IU 2x/wk
8,000 IU 3x/wk	10,000 IU 3x/wk	10,000 IU 2x/wk
10,000 IU 3x/wk	Contact nephrologist	8,000 IU 3x/wk

NORTHERN RENAL PROGRAM

DOSE ADJUSTMENT SCHEDULE FOR PATIENTS USING ARANESP (DARBEPOIETIN)

The following chart provides the necessary changes for most dose increments or dose reductions If the patient's dosing does not fall into one of the intervals, contact the nephrologist

The following Aranesp pre-filled syringes are available

- 10 mcg
- 20 mcg
- 30 mcg
- 40 mcg
- 50 mcg
- 60 mcg
- 80 mcg
- 100 mcg and
- 150 mcg

Current Dose/WK	**Increase Dose To**	**Reduce Dose To**
10 mcg/q2wk	10 mcg/wk	Discontinue Aranesp™
10 mcg/wk	20 mcg/wk	10 mcg/q2wk
20 mcg/wk	30 mcg/wk	10 mcg/wk
30 mcg/wk	40 mcg/wk	20 mcg/wk
40 mcg/wk	50 mcg/wk	30 mcg/wk
50 mcg/wk	60 mcg/wk	40 mcg/wk
60 mcg/wk	80 mcg/wk	50 mcg/wk
80 mcg/wk	100 mcg/wk	60 mcg/wk
100 mcg/wk	150 mcg/wk	80 mcg/wk
150 mcg/wk	Contact nephrologist	100 mcg/wk

Appendix B

BC Renal Agency
Room 620-16 10S Burrard Str-
Vancouver BC V6Z 1
Tel (604) 631 34 Fax (604) 6_1 3_
e mail acpra@renalbc.bc.ca

Consent for Use of Data
Patient Record and Outcome Management Information System

As an individual requiring renal services in the Province of British Columbia, I, _____ understand that information regarding my clinical, laboratory, and treatment regimens will be entered in a provincial database This information will not be accessible by any members of the public and will remain anonymous This information may be used for statistical purposes, but I will not be identified as an individual at any time

The purpose of this information is to ensure state of the art delivery of care and to provide my caregivers with efficient, timely and accurate information about my health today and into the future

By signing this form I acknowledge that my caregivers, the statistical analysts and data managers in charge of the Patient Information System may have access to my personal information

_____
SIGNATURE

_____
DATE

_____
WITNESS

Appendix C

From Lee Er (Renal) [ler@bcpra ubc ca]
Sent September-03-08 9 41 AM
To sushila@shaw ca
Subject RE Anemia management study

To Whom It May Concern,

This is to confirm that any access or release of PROMIS data for research purposes will be proceeded upon the approval of the ethics board on the project A copy of the ethics' approval must be faxed to BC Renal Agency at 604-806-8005 Only data related to the research project for the prespecified hospital/region, without any subject identifier information (e g PHN, Names, Date of Birth), will be released

Thank you,

Mirek Piaseczny
Director of Information and Statistics
BC Renal Agency
An agency of the Provincial Health Services Authority
570 14 - 1081 Burrard Street
Vancouver, BC, V6Z 1Y6
tel (604)806-8647
fax (604)806-8005

Appendix D

UNIVERSITY OF NORTHERN BRITISH COLUMBIA

RESEARCH ETHICS BOARD

MEMORANDUM

To: Sushila Saunders
CC: Martha MacLeod

From: Henry Harder, Chair
Research Ethics Board

Date. June 8, 2009

Re: **E2009.0602.094**
Anemia management protocols in the care of hemodialysis patients
Examining patient outcomes

Thank you for submitting the above-noted proposal to the Research Ethics Board Your proposal has been approved

We are pleased to issue approval for the above named study for a period of 12 months from the date of this letter Continuation beyond that date will require further review and renewal of REB approval Any changes or amendments to the protocol or consent form must be approved by the Research Ethics Board

Good luck with your research

Sincerely,

Henry Harder

Appendix E

Northern Health Corporate Office
600-299 Victoria Street, Prince George, BC V2L 5B8
Telephone (250) 565-2649, Fax (250) 565-2640, www northernhealth ca

June 29, 2009 File #RRC-2009-0020

Sushila Saunders
4435 Otway Rd
Prince George BC V2M 6X6

Dear Sushila

RE: Anemia management protocols in the care of hemodialysis patients: Examining patient outcomes

On behalf of the Northern Health Research Review Committee, I would like to thank you for your submission titled

"Anemia management protocols in the care of hemodialysis patients Examining patient outcomes"

Your study has met the requirements of the Northern Health Research Review Committee and you may proceed

Enjoy your work! We look forward to hearing about your findings

Sincerely,

Suzanne Johnston, Chair, NH Research Review Committee
Vice President, Academic Affairs and Chief Nursing Officer
SJ/sw
CC Laurie Ledger
File

Appendix F

Levene's test for Equality of Variances for Hgb t-test

Month	*F*	*p*
October mean Hgb	1 127	291
November mean Hgb	1 975	163
December mean Hgb	341	561
January mean Hgb	042	837
February mean Hgb	071	790
March mean Hgb	1 559	215
April mean Hgb	456	501
May mean Hgb	687	409
June mean Hgb	611	436
July mean Hgb	1 029	313
August mean Hgb	321	572
September mean Hgb	3 146	079

Effect Size of the Difference Between the Means of Hemoglobin Levels

Month	Mean difference	SD	Cohen's d
October	-1 40	15 18	09
November	- 43	14 00	03
December	3 43	13 17	26
January	- 27	14 12	02
February	3 63	14 10	26
March	01	14 16	01
April	-1 85	13 19	14
May	93	14 37	06
June	99	14 07	07
July	-1 97	12 70	16
August	-1 69	12 07	14
September	-3 11	12 71	24

Independent Samples t-test for Equality of Means

Month		*t*	*df*	*p* (2 tailed)
October mean Hgb	Equal variances assumed	- 488	100	627
November mean Hgb	Equal variances assumed	- 165	100	870
December mean Hgb	Equal variances assumed	1 009	80	316
January mean Hgb	Equal variances assumed	- 097	101	923
February mean Hgb	Equal variances assumed	1 326	100	188
March mean Hgb	Equal variances assumed	003	86	997
April mean Hgb	Equal variances assumed	- 700	94	485
May mean Hgb	Equal variances assumed	340	102	735
June mean Hgb	Equal variances assumed	346	94	730
July mean Hgb	Equal variances assumed	- 723	88	472
August mean Hgb	Equal variances assumed	- 635	87	527
September mean Hgb	Equal variances assumed	-1 265	99	209

Appendix G

Hemoglobin Categories-October

		75-109	110-125	126-145	Total
Control group	Count	22	27	10	59
	Expected Count	21 2	27 7	10 0	59 0
	% within case	37 3	45 8	16 9	100 0
	% within Oct Hgb	61 1	57 4	58 8	59 0
	% of Total	22 0	27 0	10 0	59 0
Protocol group	Count	14	20	7	41
	Expected Count	14 8	19 3	7 0	41 0
	% within case	34 1	48 8	17 1	100 0
	% within Oct Hgb	38 9	42 6	41 2	41 0
	% of Total	14 0	20 0	7 0	41 0

Hemoglobin Categories-November

		75-109	110-125	126-145	Total
Control group	Count	18	30	13	61
	Expected Count	16 7	32 9	11 4	61 0
	% within case	29 5	49 2	21 3	100 0
	% within Nov_Hgb	64 3	54 5	68 4	59 8
	% of Total	17 6	29 4	12 7	59 8
Protocol group	Count	10	25	6	41
	Expected Count	11 3	22 1	7 6	41 0
	% within case	24 4	61 0	14 6	100 0
	% within Nov_Hgb	35 7	45 5	31 6	40 2
	% of Total	9 8	24 5	5 9	40 2

Hemoglobin Categories- December

		75-109	110-125	126-145	Total
Control group	Count	18	27	13	58
	Expected Count	19 8	25 0	13 2	58 0
	% within case	31 0	46 6	22 4	100 0
	% within Dec_Hgb	66 7	79 4	72 2	73 4
	% of Total	22 8	34 2	16 5	73 4
Protocol group	Count	9	7	5	21
	Expected Count	7 2	9 0	4 8	21 0
	% within case	42 9	33 3	23 8	100 0
	% within Dec_Hgb	33 3	20 6	27 8	26 6
	% of Total	11 4	8 9	6 3	26 6

Hemoglobin Categories-January

		75-109	110-125	126-145	Total
Control group	Count	17	25	17	59
	Expected Count	16 9	24 7	17 5	59 0
	% within case	28 8	42 4	28 8	100 0
	% within Jan_Hgb	60 7	61 0	58 6	60 2
	% of Total	17 3	25 5	17 3	60 2
Protocol group	Count	11	16	12	39
	Expected Count	11 1	16 3	11 5	39 0
	% within case	28 2	41 0	30 8	100 0
	% within Jan_Hgb	39 3	39 0	41 4	39 8
	% of Total	11 2	16 3	12 2	39 8

Hemoglobin Categories- February

		75-109	110-125	126-145	Total
Control group	Count	14	30	13	57
	Expected Count	14 5	30 2	12 2	57 0
	% within case	24 6	52 6	22 8	100 0
	% within Feb_Hgb	56 0	57 7	61 9	58 2
	% of Total	14 3	30 6	13 3	58 2
Protocol group	Count	11	22	8	41
	Expected Count	10 5	21 8	8 8	41 0
	% within case	26 8	53 7	19 5	100 0
	% within Feb_Hgb	44 0	42 3	38 1	41 8
	% of Total	11 2	22 4	8 2	41 8

Hemoglobin Categories- March

		75-109	110-125	126-145	Total
Control group	Count	17	26	17	60
	Expected Count	15 9	29 0	15 2	60 0
	% within case	28 3	43 3	28 3	100 0
	% within Mar_Hgb	73 9	61 9	77 3	69 0
	% of Total	19 5	29 9	19 5	69 0
Protocol group	Count	6	16	5	27
	Expected Count	7 1	13 0	6 8	27 0
	% within case	22 2	59 3	18 5	100 0
	% within Mar_Hgb	26 1	38 1	22 7	31 0
	% of Total	6 9	18 4	5 7	31 0

Hemoglobin Categories- April

		75-109	110-125	126-145	Total
Control group	Count	15	31	14	60
	Expected Count	14 4	30 6	15 0	60 0
	% within case	25 0	51 7	23 3	100 0
	% within Apr_Hgb	65 2	63 3	58 3	62 5
	% of Total	15 6	32 3	14 6	62 5
Protocol group	Count	8	18	10	36
	Expected Count	8 6	18 4	9 0	36 0
	% within case	22 2	50 0	27 8	100 0
	% within Apr_Hgb	34 8	36 7	41 7	37 5
	% of Total	8 3	18 8	10 4	37 5

Hemoglobin Categories-May

		75-109	110-125	126-145	Total
Control group	Count	17	29	14	60
	Expected Count	17 2	30 9	11 9	60 0
	% within case	28 3	48 3	23 3	100 0
	% within May_Hgb	58 6	55 8	70 0	59 4
	% of Total	16 8	28 7	13 9	59 4
Protocol group	Count	12	23	6	41
	Expected Count	11 8	21 1	8 1	41 0
	% within case	29 3	56 1	14 6	100 0
	% within May_Hgb	41 4	44 2	30 0	40 6
	% of Total	11 9	22 8	5 9	40 6

Hemoglobin Categories-June

		75-109	110-125	126-145	Total
Control group	Count	22	24	14	60
	Expected Count	22 1	23 4	14 5	60 0
	% within case	36 7	40 0	23 3	100 0
	% within Jun_Hgb	62 9	64 9	60 9	63 2
	% of Total	23 2	25 3	14 7	63 2
Protocol group	Count	13	13	9	35
	Expected Count	12 9	13 6	8 5	35 0
	% within case	37 1	37 1	25 7	100 0
	% within Jun_Hgb	37 1	35 1	39 1	36 8
	% of Total	13 7	13 7	9 5	36 8

Hemoglobin Categories-July

		75-109	110-125	126-145	Total
Control group	Count	22	26	13	61
	Expected Count	22 4	25 8	12 9	61 0
	% within case	36 1	42 6	21 3	100 0
	% within Jul_Hgb	66 7	68 4	68 4	67 8
	% of Total	24 4	28 9	14 4	67 8
Protocol group	Count	11	12	6	29
	Expected Count	10 6	12 2	6 1	29 0
	% within case	37 9	41 4	20 7	100 0
	% within Jul_Hgb	33 3	31 6	31 6	32 2
	% of Total	12 2	13 3	6 7	32 2
	% of Total	36 7	42 2	21 1	100 0

Hemoglobin Categories-August

		75-109	110-125	126-145	Total
Control group	Count	22	27	9	58
	Expected Count	20 0	27 3	10 7	58 0
	% within case	37 9	46 6	15 5	100 0
	% within Aug_Hgb	73 3	65 9	56 3	66 7
	% of Total	25 3	31 0	10 3	66 7
Protocol group	Count	8	14	7	29
	Expected Count	10 0	13 7	5 3	29 0
	% within case	27 6	48 3	24 1	100 0
	% within Aug_Hgb	26 7	34 1	43 8	33 3
	% of Total	9 2	16 1	8 0	33 3

Hemoglobin Categories-September

		75-109	110-125	126-145	Total
Control group	Count	24	25	12	61
	Expected Count	20 1	29 9	11 0	61 0
	% within case	39 3	41 0	19 7	100 0
	% within Sep_Hgb	72 7	51 0	66 7	61 0
	% of Total	24 0	25 0	12 0	61 0
Protocol group	Count	9	24	6	39
	Expected Count	12 9	19 1	7 0	39 0
	% within case	23 1	61 5	15 4	100 0
	% within Sep_Hgb	27 3	49 0	33 3	39 0
	% of Total	9 0	24 0	6 0	39 0

Chi-Square Test of Lower than, on Target and Higher than Target Hemoglobin Data

Month	*n*	Chi-Square value	*df*	*p* (2 sided)
October	100	133	2	945
November	102	1 454	2	483
December	79	1 270	2	530
January	98	044	2	978
February	98	174	2	917
March	87	1 951	2	377
April	96	262	2	877
May	101	1 223	2	542
June	95	099	2	951
July	90	029	2	985
August	87	1 393	2	498
September	100	4 200	2	122

Appendix H

On/Off Target Hemoglobin Categories-October

		110-125	<110 or >125	Total
Control group	Count	27	34	61
	Expected Count	28 1	32 9	61 0
	% within case	44 3	55 7	100 0
	% within October target	57 4	61 8	59 8
	% of Total	26 5	33 3	59 8
Protocol group	Count	20	21	41
	Expected Count	18 9	22 1	41 0
	% within case	48 8	51 2	100 0
	% within October target	42 6	38 2	40 2
	% of Total	19 6	20 6	40 2

On/Off Target Hemoglobin Categories-November

		110-125	<110 or > 125	Total
Control group	Count	30	31	61
	Expected Count	32 9	28 1	61 0
	% within case	49 2	50 8	100 0
	% within November target	54 5	66 0	59 8
	% of Total	29 4	30 4	59 8
Protocol group	Count	25	16	41
	Expected Count	22 1	18 9	41 0
	% within case	61 0	39 0	100 0
	% within November target	45 5	34 0	40 2
	% of Total	24 5	15 7	40 2

On/Off Target Hemoglobin Categories December

		110-125	<110 or > 125	Total
Control group	Count	27	34	61
	Expected Count	25 3	35 7	61 0
	% within case	44 3%	55 7%	100 0%
	% within December target	79 4%	70 8%	74 4%
	% of Total	32 9%	41 5%	74 4%
Protocol group	Count	7	14	21
	Expected Count	8 7	12 3	21 0
	% within case	33 3%	66 7%	100 0%
	% within December target	20 6%	29 2%	25 6%
	% of Total	8 5%	17 1%	25 6%

On/Off Target Hemoglobin Categories-January

		110-125	<110 or > 125	Total
Control group	Count	25	36	61
	Expected Count	24 3	36 7	61 0
	% within case	41 0%	59 0%	100 0%
	% within January target	61 0%	58 1%	59 2%
	% of Total	24 3%	35 0%	59 2%
Protocol group	Count	16	26	42
	Expected Count	16 7	25 3	42 0
	% within case	38 1%	61 9%	100 0%
	% within January target	39 0%	41 9%	40 8%
	% of Total	15 5%	25 2%	40 8%

On/Off Target Hemoglobin Categories-February

		110-125	<110 or > 125	Total
Control group	Count	30	30	60
	Expected Count	30 6	29 4	60 0
	% within case	50 0%	50 0%	100 0%
	% within Feb target	57 7%	60 0%	58 8%
	% of Total	29 4%	29 4%	58 8%
Protocol group	Count	22	20	42
	Expected Count	21 4	20 6	42 0
	% within case	52 4%	47 6%	100 0%
	% within Feb target	42 3%	40 0%	41 2%
	% of Total	21 6%	19 6%	41 2%

On/Off Target Hemoglobin Categories March

		110-125	<110 or > 125	Total
Control group	Count	26	35	61
	Expected Count	29 1	31 9	61 0
	% within case	42 6%	57 4%	100 0 %
	% within March target	61 9%	76 1%	69 3%
	% of Total	29 5%	39 8%	69 3%
Protocol group	Count	16	11	27
	Expected Count	12 9	14 1	27 0
	% within case	59 3%	40 7%	100 0 %
	% within March target	38 1%	23 9%	30 7%
	% of Total	18 2%	12 5%	30 7%

On/Off Target Hemoglobin Categories-April

		110-125	<110 or > 125	Total
Control group	Count	31	29	60
	Expected Count	30 6	29 4	60 0
	% within case	51 7%	48 3%	100 0%
	% within April target	63 3%	61 7%	62 5%
	% of Total	32 3%	30 2%	62 5%
Protocol group	Count	18	18	36
	Expected Count	18 4	17 6	36 0
	% within case	50 0%	50 0%	100 0%
	% within April target	36 7%	38 3%	37 5%
	% of Total	18 8%	18 8%	37 5%

On/Off Target Hemoglobin Categories-May

		110-125	<110 or > 125	Total
Control group	Count	29	32	61
	Expected Count	30 5	30 5	61 0
	% within case	47 5%	52 5%	100 0%
	% within May target	55 8%	61 5%	58 7%
	% of Total	27 9%	30 8%	58 7%
Protocol group	Count	23	20	43
	Expected Count	21 5	21 5	43 0
	% within case	53 5%	46 5%	100 0%
	% within May target	44 2%	38 5%	41 3%

On/Off Target Hemoglobin Categories June

		110-125	<110 or > 125	Total
Control group	Count	24	37	61
	Expected Count	23 5	37 5	61 0
	% within case	39 3%	60 7%	100 0%
	% within June target	64 9%	62 7%	63 5%
	% of Total	25 0%	38 5%	63 5%
Protocol group	Count	13	22	35
	Expected Count	13 5	21 5	35 0
	% within case	37 1%	62 9%	100 0%
	% within June target	35 1%	37 3%	36 5%
	% of Total	13 5%	22 9%	36 5%

On/Off Target Hemoglobin Categories July

		110-125	<110 or > 125	Total
Control group	Count	26	35	61
	Expected Count	25 8	35 2	61 0
	% within case	42 6%	57 4%	100 0%
	% within July target	68 4%	67 3%	67 8%
	% of Total	28 9%	38 9%	67 8%
Protocol group	Count	12	17	29
	Expected Count	12 2	16 8	29 0
	% within case	41 4%	58 6%	100 0%
	% within July target	31 6%	32 7%	32 2%
	% of Total	13 3%	18 9%	32 2%

On/Off Target Hemoglobin Categories August

		110-125	<110 or > 125	Total
Control group	Count	27	31	58
	Expected Count	26 7	31 3	58 0
	% within case	46 6%	53 4%	100 0%
	% within August target	65 9%	64 6%	65 2%
	% of Total	30 3%	34 8%	65 2%
Protocol group	Count	14	17	31
	Expected Count	14 3	16 7	31 0
	% within case	45 2%	54 8%	100 0%
	% within August target	34 1%	35 4%	34 8%
	% of Total	15 7%	19 1%	34 8%

On/Off Target Hemoglobin Categories September

		110-125	< 110 or > 125	Total
Control group	Count	25	36	61
	Expected Count	29 6	31 4	61 0
	% within case	41 0%	59 0%	100 0%
	% within September target	51 0%	69 2%	60 4%
	% of Total	24 8%	35 6%	60 4%
Protocol group	Count	24	16	40
	Expected Count	19 4	20 6	40 0
	% within case	60 0%	40 0%	100 0%
	% within September target	49 0%	30 8%	39 6%
	% of Total	23 8%	15 8%	39 6%

Chi-Square Test of On/Off Categorical Hemoglobin Data

Month	*n*	Chi-Square value	*df*	*p* (2 sided)
October	102	0 201	1	654
November	102	1 373	1	241
December	82	0 769	1	381
January	103	0 087	1	769
February	102	0 056	1	813
March	88	2 076	1	150
April	96	0 025	1	874
May	104	0 357	1	550
June	96	0 046	1	831
July	90	0 012	1	911
August	89	0 016	1	900
September	101	3 498	1	061

Appendix I

Levene's Test for Equality of Variances for Epoetin Alfa Mean Dose in Control and Protocol Groups

Month	Equal variances	*F*	*p*
October mean Epoetin Alfa dose	assumed	1 454	231
November mean Epoetin Alfa dose	assumed	2 262	136
December mean Epoetin Alfa dose	assumed	2 639	108
January mean Epoetin Alfa dose	assumed	2 063	154
February mean Epoetin Alfa dose	assumed	3 857	053
March mean Epoetin Alfa dose	assumed	2 850	095
April mean Epoetin Alfa dose	not assumed	7 677	007
May mean Epoetin Alfa dose	not assumed	8 364	005
June mean Epoetin Alfa dose	not assumed	4 749	032
July mean Epoetin Alfa dose	assumed	3 072	083
August mean Epoetin Alfa dose	assumed	2 246	137
September mean Epoetin Alfa dose	assumed	2 240	138

Effect Size of the Difference Between the Means of Epoetin Alfa

Month	Mean difference	SD	Cohen's *d*
October	1 14	3 00	38
November	1 12	3 11	36
December	1 52	3 08	49
January	-1 25	3 19	39
February	-4 08	3 24	1 26
March	-5 86	3 34	1 75
April	-1 02	3 28	32
May	-1 03	3 31	31
June	-1 11	3 30	34
July	-1 07	3 35	32
August	-1 05	3 40	31
September	-9 41	3 38	2 78