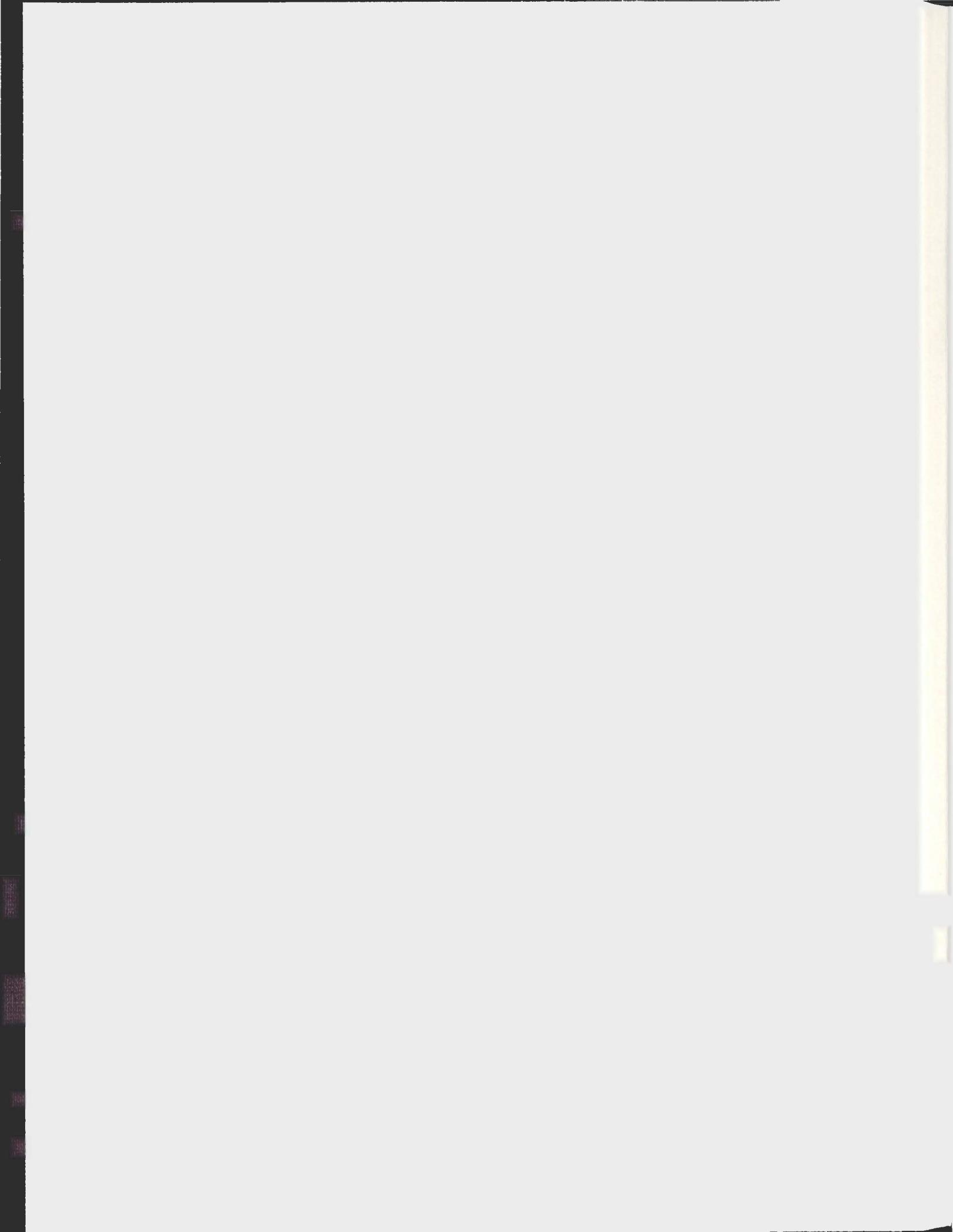


A RANDOMIZED CONTROLLED TRIAL OF COSTS  
ASSOCIATED WITH ANEMIA THERAPY IN HEMODIALYSIS  
PATIENTS TREATED WITH INTRAVENOUS DARBEPOETIN ALFA  
VERSUS INTRAVENOUS EPOETIN ALFA

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**A Randomized Controlled Trial of Costs Associated with Anemia Therapy in  
Hemodialysis Patients Treated with Intravenous Darbepoetin alfa versus  
Intravenous Epoetin alfa**

by

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## **ABSTRACT**

Anemia of Chronic Kidney Disease is associated with adverse cardiovascular and clinical outcomes and a reduced quality of life. Erythropoiesis stimulating agents (ESAs) have improved anemia management and two agents are available in Canada, epoetin alfa (Eprex®) and darbepoetin alfa (Aranesp®). Darbepoetin requires less frequent administration due to a longer half-life. Epoetin and darbepoetin are considered to be equally effective in achieving target hemoglobin in dialysis patients but it is not clear if there is a cost difference. There have been few head-to-head comparisons of the two ESAs; most published data is from observational switch studies.

An open label randomized controlled trial of intravenous darbepoetin alfa versus epoetin alfa was conducted in hemodialysis patients. Fifty patients were enrolled in the study. A dose stabilization run-in phase was followed by a 12 month active phase. ESAs and iron were dosed using a study algorithm to maintain hemoglobin within 100-120g/L. The primary outcome was the cost per patient of ESA over 12 months. Secondary outcomes included deviation from target ranges in anemia indices, iron dose and cost, time and number of dose changes required for dose stabilization, number of dose changes in the active phase and the dose conversion ratio.

The median cost for epoetin over 12 months was \$4179(IQR \$2416-5955) and for darbepoetin was \$2303(IQR \$1178-4219) with a difference of \$1876 (p=0.017). There was no significant difference in the dose or cost of iron. The median weekly iron dose

was 40.4mg for epoetin and 41.7mg for darbepoetin ( $p=0.992$ ). There were no significant differences in the anemia care targets including hemoglobin: 108.0g/L epoetin and 109.8g/L darbepoetin ( $p=0.336$ ); serum ferritin: 848 $\mu$ g/L epoetin and 726 $\mu$ g/L darbepoetin ( $p=0.202$ ); TSAT: 26.7% epoetin and 28.6% darbepoetin ( $p=0.472$ ).

The number of dose changes and the time required to attain hemoglobin stability in the run-in phase and the number of dose changes in the active phase were similar for both groups. The dose conversion ratio was 280:1 (95% CI 197-362:1) at the end of the run-in phase, 360:1 (95% CI 262-457:1) at the 3 month point of the active phase and 382:1 (95% CI 235-529:1) at the 6 month point of the active phase.

In this study of hemodialysis patients with comparable anemia management, darbepoetin cost \$1876 less per year per patient than epoetin. This difference represents a significant cost savings which would be of interest to clinicians, policy makers and payers.

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## List of Symbols, Nomenclature or Abbreviations

$\alpha$ : alfa

$\beta$ : beta

CADTH: Canadian Agency for Drugs and Technology in Health

CBC: complete blood count

CKD: Chronic Kidney Disease

CSN: Canadian Society of Nephrology

ESA: erythropoiesis stimulating agent

GFR: glomerular filtration rate

Hb: hemoglobin

HD: hemodialysis

HREA: Health Research Ethics Authority

IQR: interquartile range

IU: international units

IV: intravenous

KDIGO: Kidney Disease Improving Global Outcomes

KDOQI: Kidney Foundation Disease Outcomes Quality Initiative

ns: not statistically significant

$\mu\text{g}$ : micrograms

rHuEPO: recombinant human erythropoietin

RPAC: Research Proposals Approval Committee

SC: subcutaneous

TSAT: transferrin saturation

PD: peritoneal dialysis

PTH: parathyroid hormone

SD: standard deviation

¥: yen

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## Chapter 1 Introduction

### 1.1 Anemia in Chronic Kidney Disease

Anemia occurs when there is a lower than normal number of circulating red blood cells which is usually measured by a decrease in the amount of hemoglobin in the blood. Anemia may be caused by nutritional deficiencies, may be drug-induced or may be associated with chronic diseases.<sup>1</sup>

Anemia is one of the earliest, most characteristic, and morbid manifestations of Chronic Kidney Disease (CKD) and is often present before the onset of uremic symptoms. It is generally a normochromic, normocytic anemia.<sup>2</sup> The severity and prevalence of anemia increases as CKD progresses and is present in most patients with a glomerular filtration rate (GFR) between 30-40mL/min, but may also occur with higher GFRs. Anemia of CKD is associated with left ventricular hypertrophy, adverse cardiovascular and clinical outcomes and a reduction in quality of life.<sup>3,4</sup>

While a number of factors may contribute to the development of anemia in CKD including iron deficiency, blood loss, inflammation, secondary hyperparathyroidism and shortened red blood cell survival, decreased erythropoietin production by the kidney is the principal cause. Erythropoiesis is the process by which red blood cells are produced in the body. Red blood cells are critical as they contain hemoglobin, which is a vital iron-containing molecule that carries oxygen between the lungs and

tissues. When oxygen levels are decreased in the blood, a glycoprotein hormone called erythropoietin is released which acts on the bone marrow to stimulate reticulocyte (red blood cell precursor) production. The kidney is the primary site of erythropoietin production (90%), with a small contribution from the liver, making it unique amongst the hematopoietic growth factors as it is not produced in the bone marrow. The kidney acts as a hematocrit meter in that it detects oxygen tension and extracellular volume and it regulates red cell mass through production and release of erythropoietin and plasma volume through excretion of salt and water. In this process, it maintains the hematocrit at a normal value of 45% which maximizes oxygen delivery to the peripheral tissues. As kidney function declines, so does the production of erythropoietin with subsequent progressive anemia.<sup>2, 5</sup>

## 1.2 Management of Anemia – Iron

Adequate iron is essential for erythropoiesis as it is needed to produce hemoglobin. Iron deficiency requiring supplementation is common in hemodialysis patients. In the initial assessment of anemia in CKD, iron status should be assessed with serum ferritin (a surrogate marker for tissue iron stores) and transferrin saturation (TSAT - represents iron which is available for erythropoiesis) with consideration of the mean corpuscular volume (which is a late marker of iron deficiency). It is important to note that interpretation of ferritin levels alone is difficult because ferritin is an acute-phase reactant and can be elevated for reasons other than high tissue iron stores. Some argue

that transferrin saturation is a more reliable measure as it is not influenced by inflammatory states.<sup>6</sup>

The Canadian Society of Nephrology (CSN) in their current Clinical Practice Guidelines recommend that in hemodialysis patients iron should be administered intravenously to maintain serum ferritin >200ng/mL and TSAT >20%.<sup>7</sup> Absolute iron deficiency occurs when both the ferritin and TSAT are below the target values.

Functional iron deficiency may also occur in hemodialysis patients, in which case the serum ferritin is above 200ng/mL (and is often in the upper end of the acceptable range or higher) but the TSAT is below 20%. In functional iron deficiency, there is an apparent inability to mobilize iron stores.<sup>8</sup> While the safety of administering iron when the serum ferritin is above 500ng/mL is not clear, there is some evidence from the DRIVE<sup>9</sup> trial that when the TSAT is concomitantly low intravenous iron can increase the hemoglobin level, though this study was not powered to assess safety. As iron therapy has not been tested by large randomized trials with important clinical outcomes, the CSN currently recommends that the risk and benefit of continued iron administration when the serum ferritin level is above 800ng/mL should be carefully considered in each patient.<sup>7</sup>

In the Fall of 2012, the KDIGO (Kidney Disease Improving Global Outcomes) Anemia Work Group published clinical practice guidelines for the management of anemia in CKD.<sup>10</sup> In these it is recommended to balance the potential benefits of iron therapy with risks of harm in individual patients (acute reactions and unknown long-

term risks). More specifically in adult CKD patients not already on ESA or iron, they recommend a trial of intravenous iron if an increase in Hb is desired and the TSAT is  $\leq 30\%$  and ferritin is  $\leq 500\text{ng/mL}$ . For adult CKD patients on ESA and not on iron, they recommend intravenous iron if an increase in Hb or a decrease in ESA dose is desired and the TSAT is  $\leq 30\%$  and ferritin is  $\leq 500\text{ng/mL}$ .

### 1.3 Management of Anemia - Erythropoiesis Stimulating Agents

Erythropoiesis stimulating agents (ESAs) are proteins which stimulate erythropoiesis by the same mechanism as endogenous erythropoietin. The development of these drugs was a major advance and since the first agent came to market in 1989 the management of anemia in CKD has improved dramatically as previously the main therapeutic option was red blood cell transfusions.<sup>3</sup> When epoetin was first used clinically it was primarily in long-term, transfusion-dependent hemodialysis patients with the goal of alleviating symptoms and decreasing transfusions and potential transfusion complications. ESA use eventually extended to most dialysis patients with anemia and to stages 4 and 5 CKD patients. Complete correction of anemia was initially expected to be beneficial for patients with respect to left ventricular hypertrophy, cardiovascular outcomes, hospital admissions and death based on early observational studies. However, as clinical trials were conducted in large groups it became apparent that complete correction of anemia to normal hemoglobin levels does not offer cardiovascular benefits and in fact may be harmful with respect to increased risk of stroke, vascular access problems and hypertension with modest or questionable improvements in quality of life. In the recently published guidelines for

anemia management, KDIGO recommends that when using ESA therapy clinicians should consider and balance the benefit of reduced blood transfusions and anemia related symptoms against the risk of harm in individual patients. In addition, they recommend using ESAs with great caution, if at all, in CKD patients with active malignancy, a history of stroke, or a history of malignancy.<sup>10</sup> This recommendation was based primarily on outcomes of ESA use in the oncology population. Of note, in a post-hoc analysis of the TREAT study<sup>11</sup> of ESA use in CKD patients there was a significantly higher death rate from cancer in patients with a history of malignancy in the darbepoetin arm compared to the placebo arm.

The current CSN Clinical Practice Guidelines state that ESAs should be used to treat anemia when iron stores are replete, other causes of anemia have been addressed and the hemoglobin is sustained below 100g/L. The CSN recommends a target hemoglobin of 110g/L, with an acceptable range of 100-120g/L.<sup>4</sup>

With respect to anemia targets, the new KDIGO clinical practice guidelines for anemia management recommend that ESA therapy be initiated in adult dialysis patients when the Hb is between 90-100g/L to avoid having the Hb fall below 90g/L. It is also recommended in general to not use ESAs to maintain Hb above 115g/L, and to never use them to increase Hb above 130g/L. The KDIGO guidelines suggest an individualized approach to determining targets may be necessary in some patients.<sup>10</sup>

Endogenous erythropoietin consists of a polypeptide core of 165 amino acids with four glycosylation sites that carry three N-linked and one O-linked oligosaccharide chain. The receptor binding sites are localized at one end of the molecule, distant from the glycosylation sites. The three N-linked chains may contain 2-4 oligosaccharide branches, each terminated with a sialic acid. The O-linked chain carries up to two sialic acid residues. The biologic activity of erythropoietin is largely determined by the N-linked carbohydrate residues.<sup>12</sup>

Epoetin was first marketed in 1989 and is a recombinant human erythropoietin (r-HuEPO) which is composed of the same amino acid sequence with three N-linked carbohydrate chains as endogenous erythropoietin but the glycosylation varies. There are two commercially available epoetin types –  $\alpha$  (Eprex®, Procrit®) and  $\beta$  (Recormon®, Neorecormon®). These are produced by Chinese hamster ovary cells and contain a higher proportion of sialylated, acidic carbohydrate residues than endogenous erythropoietin. Epoetin  $\beta$  has a higher molecular weight than  $\alpha$  and is available in some European and other countries but is not marketed in the US or Canada. In Canada, epoetin  $\alpha$  is available as Eprex® only. There are no significant clinical differences between epoetin  $\alpha$  and  $\beta$ .<sup>12</sup>

Darbepoetin alfa was approved for use in 2001 for anemia of CKD. Darbepoetin is also produced in Chinese hamster ovary cells.<sup>12</sup> It differs from epoetin in that it has a higher molecular weight and contains two additional N-linked carbohydrate chains and the increased sialylated carbohydrate content results in a longer half-life and

sustained biologic activity.<sup>13</sup> Darbepoetin has a lower binding affinity for the erythropoietin receptor than epoetin alfa in vitro and takes 3-5 times longer to reach peak serum concentrations.<sup>14</sup>

Darbepoetin has a three-fold longer half life than epoetin when administered intravenously with half-lives of 25.3 hours and 8.5 hours respectively. When given subcutaneously, the half-lives are 48.8 hours and 16-24 hours.<sup>15-17</sup> Based on this, darbepoetin is administered once weekly or once every two weeks, whereas epoetin should be given in multiple weekly injections (most often three).

Epoetin appears to require higher doses when it is administered less frequently.<sup>18</sup> It was found in a study in the United Kingdom of hemodialysis patients that both epoetin and darbepoetin could maintain hemoglobin targets when administered once weekly, but the dose of epoetin required was higher when given once weekly as compared to three times weekly.<sup>19</sup> The CSN currently recommends that epoetin should be given three times weekly as reduced dosing frequency may lead to increased dose requirements.<sup>4</sup>

Epoetin was reported to require higher doses when administered intravenously than subcutaneously in a meta-analysis of 27 comparative studies involving 916 hemodialysis patients.<sup>20</sup> In a pharmacokinetic study of darbepoetin, it was found that the intravenous and subcutaneous doses are the same, and that this was likely due to its longer terminal half-life than epoetin.<sup>16</sup> In a prospective, noninferiority trial of

epoetin versus darbepoetin (IV and SC) in dialysis patients, it was found that the intravenous and subcutaneous doses of darbepoetin did not differ over the 52 week study period, whereas in the epoetin group the dose requirements for subcutaneous administration were 22% less than for intravenous administration.<sup>21</sup>

#### 1.4 Dose Conversion

Based on peptide mass, 200 IU (international units) of epoetin  $\alpha$  is equivalent to 1  $\mu$ g of darbepoetin  $\alpha$ .<sup>12</sup> As a result, when darbepoetin came to market and patients were first converted from epoetin, it was recommended by the manufacturer to determine the initial darbepoetin dose based on a fixed ratio of 200:1 (epoetin:darbepoetin).<sup>22</sup>

As this ratio was employed in studies it became apparent that it was not accurate in all dose ranges and for all indications and in most cases darbepoetin was found to be more potent on a protein mass basis than epoetin. A combined analysis of three studies in dialysis patients found that the linear relationship between epoetin and darbepoetin doses becomes curvilinear at higher doses of epoetin, particularly above 7000 units weekly when less darbepoetin was required than the 200:1 ratio would predict. The ratio was found to continue to increase with higher epoetin doses.<sup>1, 21, 23</sup>

Several other studies found the 200:1 ratio to result in excessive darbepoetin doses.<sup>15, 19, 24-31</sup> This evidence of a nonproportional dose relationship prompted the manufacturer to develop a conversion chart in which the conversion ratios recommended vary widely within the dose categories (Table 1). It is worth noting that doses above 30 000 units weekly of epoetin alfa are not typically used in treatment of anemia of CKD, so the higher dose conversion recommendations have not been

included in this table. Also, the smallest available pre-filled syringe of darbepoetin is 10µg, so a 6.25µg dose is not practically possible.

**Table 1: Aranesp® Dose Conversion Chart and Subsequent Dose Ratio Range<sup>23</sup>**

Previous Weekly Epoetin alfa Dose (units/week)	Manufacturer Recommended Weekly Darbepoetin Dose (µg/week)	Dose Ratio Range
<2500	6.25	400:1
2500-4999	12.5	200:1 - 400:1
5000-10 999	25	200:1 - 440:1
11 000-17 999	40	275:1 - 450:1
18 000-33 999	60	300:1 - 567:1

When studies have been conducted using the manufacturer's conversion table, it has been found that the recommendations for higher epoetin doses resulted in inadequate darbepoetin doses. In one Canadian study where hemodialysis patients were switched from epoetin to darbepoetin it was determined that for epoetin doses above 17 000 units weekly, the darbepoetin dose based on the conversion chart was too low and dose increases were required. As a result, the authors developed their own dosing algorithm in which epoetin doses of 7000 units weekly or less were converted using a 200:1 ratio and epoetin doses greater than 7000 units weekly were changed using a 300:1 ratio.<sup>32</sup> In a small observational study of hemodialysis patients in the United States in which patients were converted from epoetin to darbepoetin, the conversion

table doses were insufficient and darbepoetin dose increases were required in 67% of patients.<sup>33</sup>

In 2004, the Centres for Medicare and Medicaid Services in the United States adopted a fixed conversion ratio of 330:1 for darbepoetin from epoetin. In a cost-minimization analysis in the hospital setting comparing epoetin alfa with darbepoetin, it was determined that a cost benefit with darbepoetin would only be realized in the hospital setting when the dose conversion ratio exceeded 257:1.<sup>34</sup> In most regions including this province, Aranesp® (darbepoetin) has been priced relative to Eprex® (epoetin alfa) based on the 200:1 protein mass ratio. As a result the dose conversion ratio is important in that as it increases, there are resultant cost savings with darbepoetin based on the current pricing structure. However, it is still unclear from the available evidence what the best dose conversion ratio is.

### 1.5 Significance of Research and Purpose of Study

The comparable clinical effectiveness of epoetin and darbepoetin is a major assumption of this cost minimization analysis. Epoetin and darbepoetin are considered to be equally effective in achieving target Hb in dialysis patients.<sup>35, 36</sup>

While relative potencies may differ, there is no evidence that one ESA is more effective in stimulating erythropoiesis than another.<sup>12</sup> A number of studies have demonstrated that darbepoetin is effective in correcting anemia in rHuEPO naïve patients and in maintaining hemoglobin levels in patients who are switched from epoetin. The adverse effect profiles of darbepoetin and epoetin are comparable. In

particular, thrombotic events including vascular access thrombosis, venous thrombosis and pulmonary emboli occurred in clinical studies of darbepoetin at frequencies similar to those seen in studies of epoetin.<sup>13</sup>

It is not clear if the cost associated with anemia therapy is different for patients treated with darbepoetin than with epoetin. Approximately 90% of hemodialysis patients receive ESA for anemia management and it is a costly component of care, historically averaging between \$6000-7000 annually per patient in this province. Based on billings to date in 2012, it is estimated that the cost of ESA therapy in Eastern Health will be approximately \$1 600 000 this year. In the absence of any data suggesting a clinical advantage of one ESA over the other, determining if a cost advantage exists will allow clinicians, policy makers and payers to make informed and rational decisions about the use of these costly resources.

For ESAs, drug cost is directly related to drug dosage and even small differences in potency per unit cost of ESA can translate into large differences in costs. It was recommended in a review by the Canadian Agency for Drugs and Technology in Health (CADTH) that head-to-head comparisons of epoetin and darbepoetin should be done.<sup>37</sup> As discussed later in the literature review, there have been very few head-to-head comparisons of the two ESAs. Most studies have been pre- and post-conversion comparisons in which results are difficult to interpret and apply. Many of the studies were of subcutaneous administration, which was the route most commonly used in hemodialysis patients when epoetin first became available. This practice changed

rapidly when in the late 1990s an increased incidence of pure red cell aplasia was seen in CKD patients receiving epoetin subcutaneously. As a result it was recommended that the intravenous route be used in hemodialysis patients and most patients were switched to intravenous epoetin which remains the most commonly used route in this population in Canada today. It was subsequently determined that the pure red cell aplasia was most likely caused by the leaching of polysorbate 80 from the stopper of pre-filled syringes and since this has been corrected, pure red cell aplasia occurs very rarely with subcutaneous administration of epoetin. Despite this, the manufacturer still recommends the intravenous route as the preferred route in hemodialysis patients in the Canadian product monograph.

To address the question of differential costs associated with anemia therapy, a cost minimization analysis was undertaken in an open label, parallel group, randomized controlled trial of intravenous darbepoetin alfa (Aranesp®) versus epoetin alfa (Eprex®) in hemodialysis patients. The goal was to provide stakeholders with evidence to choose between the two ESAs which are otherwise clinically equivalent to the best of our knowledge.

## Chapter 2 Review of Literature

### 2.1 Search Strategy

To determine if a cost advantage exists for darbepoetin or epoetin in the management of anemia of CKD in hemodialysis patients, the ideal study design would be a parallel group randomized controlled trial. The study would include only hemodialysis patients, would involve intravenous administration only (generally the only route used in hemodialysis patients), would be sufficiently long to see dose stabilization with darbepoetin (at least 5-6 months<sup>1, 15, 17, 32</sup>) and would use pre-defined dosing protocols for both ESA and iron to ensure a consistent approach with all subjects.

An extensive literature search was performed in PubMed using the following search terms:

- “Erythropoietin AND darbepoetin AND cost”
- “Aranesp AND Eprex AND conversion”
- “Erythropoietin, Recombinant (Mesh) AND darbepoetin alfa(substance name)AND Therapeutic Equivalency(Mesh)”

These searches were combined using “OR” and the final yield was 128 references. The same search terms were used in Embase and IPA and this did not yield any additional references. The Cochrane database provided one reference. All abstracts were reviewed for relevance to the question and after eliminating those from the oncology population, review articles, those in pre-dialysis patients, and papers about ESA use in other areas

such as surgery and cardiology, there were 25 references of interest identified. These included 3 randomized controlled trials, 9 prospective switch studies, 6 retrospective switch studies, 1 cross-sectional analysis, 3 economic studies and 3 systematic reviews. The studies are reviewed in detail below.

## 2.2 Randomized Controlled Trials

Nissenson et al published the only randomized controlled trial comparing IV darbepoetin alfa to IV epoetin alfa in hemodialysis patients with drug dose as an outcome, albeit a secondary outcome. The study was a multicenter, randomized, double-blind, noninferiority trial to determine if darbepoetin was as effective in maintaining Hb as epoetin in CKD patients on hemodialysis.<sup>1</sup> From 35 centres in the United States and 5 centres in Canada, 507 patients were randomized in a 2:1 allocation to continue epoetin alfa or to switch to darbepoetin. Those randomized to darbepoetin were switched using a 200:1 ratio (epoetin:darbepoetin). There was a 20 week titration and stabilization period followed by an 8 week evaluation period. Epoetin and darbepoetin doses were adjusted by 25% if the hemoglobin remained above or below target on 2 consecutive weekly assessments. Iron was dosed according to the individual unit policy to maintain TSAT above 20%. The primary outcome was the mean change in hemoglobin levels between baseline and the evaluation period and secondary outcomes included hemoglobin variability and drug dose. Darbepoetin was found to be as effective as epoetin in maintaining hemoglobin within a range of 90-130g/L throughout the study period and the mean changes in hemoglobin levels from baseline to the evaluation period were not significantly different between the two groups. There was no significant difference in

hemoglobin variability between the two drugs. With respect to drug doses, the authors state that mean doses of study drug were similar between baseline and the evaluation period which suggested that the 200:1 ratio used to dose darbepoetin was appropriate. The mean weekly dose of epoetin was 12 706 units at baseline and 13 639 units during the evaluation period. The mean weekly dose of darbepoetin was 63.18  $\mu\text{g}$  at baseline and 54.18  $\mu\text{g}$  during the evaluation period. The study was not designed to determine the dose ratio between the two drugs or if there was a difference in cost, however from baseline to the end there was a decrease in the darbepoetin dose and an increase in the epoetin dose.

Molina et al conducted a prospective clinical trial in Spain to assess the effectiveness and safety of changing SC epoetin alfa to either IV epoetin alfa or IV darbepoetin alfa in 112 hemodialysis patients.<sup>38</sup> A 200:1 ratio was used to determine the darbepoetin doses and follow-up was for 24 weeks. The goal was to maintain hemoglobin between 11 and 13g/dL. The outcome measured was the resistance index which was defined as the weekly dose per kilogram of weight/level of hemoglobin. In the arm switched to IV from SC epoetin, a significant increase in the resistance index was observed with mean values of 2.73 and 4.37 after 16 and 24 weeks respectively. In the arm switched to darbepoetin there was a decrease in the resistance index starting at week 8 with mean levels of 0.012, 0.018 and 0.023 at weeks 8, 16, and 24 respectively. The dose conversion factor from SC epoetin alpha to IV darbepoetin increased significantly to 1:260 by week 24.

Dolman et al published a study out of the United Kingdom in 2004 in which 217 hemodialysis patients on SC epoetin beta were randomized to once weekly SC epoetin

beta (total weekly dose given once weekly) or once weekly SC darbepoetin (using a 200:1 dose conversion ratio)<sup>19</sup>. It was an open-label prospective trial with a predefined 9 month follow up period in which doses were adjusted using a computerized decision support system and Hb and drug doses were compared between baseline and the end of follow-up. The computerized system had been in place for more than a year prior to the study start and based on monthly hemoglobin concentrations and trends advised dose changes to maintain hemoglobin between 11-12g/dL. A protocol for iron dosing was used to maintain serum ferritin between 100-500µg/L. Similar hemoglobin outcomes were found in both groups at randomization and at the end of the study. In the per protocol analysis, the mean darbepoetin dose fell from 0.59 µg /kg/week to 0.46 µg/kg/week which was a 20% dose reduction. The epoetin mean dose increased from 107.5 units/kg/week to 133.2 units/kg/week, representing a 24% increase in dose. Similar results were seen in a modified intention to treat analysis. Of the 217 subjects randomized, 169 completed the study. It was noted that dose and hemoglobin stabilization did not occur in this study until at least 28 weeks after conversion, suggesting a minimum follow-up period for similar trials is required.

The randomized controlled trials are summarized in Table 2. While these studies were not designed to test the specific research question of interest, the results of these trials seem to indicate that the 200:1 ratio for dose conversion is likely not stable and correct in the hemodialysis populations studied.

**Table 2: Randomized Controlled Trials**

	Subjects	ESA	Targets (Hb, Fe) Follow-up	Outcomes	Results
Nissenson US/Canada,2002	HD n=507	IV epoetin alfa and IV darbepoetin	Hb 90-130g/L TSAT>20%  20 week titration and 8 week evaluation	1°-mean change in Hb 2° -Hb variability, drug dose	<ul style="list-style-type: none"> <li>- Equally effective in maintaining Hb</li> <li>- darbepoetin not inferior to epoetin</li> <li>- Hb variability not different</li> <li>- Epoetin dose similar, darbepoetin dose decreased</li> </ul>
Molina Spain, 2004	HD n=112	SC epoetin alfa changed to IV epoetin alfa or IV darbepoetin	Hb 11-13g/dL  24 weeks	Resistance index  Dose conversion factor	<ul style="list-style-type: none"> <li>- Resistance index increased for epoetin</li> <li>- Resistance index decreased for darbepoetin</li> <li>- Dose conversion ratio 1:260 at week 24</li> </ul>
Dolman UK, 2004	HD n=169	SC epoetin β and SC darbepoetin	Hb 11-12g/dL Ferritin 100- 500μg/L  9 months	Hb  ESA dose	<ul style="list-style-type: none"> <li>- Similar Hb outcomes</li> <li>- Darbepoetin dose fell by 20%</li> <li>- Epoetin dose increased by 24%</li> </ul>

HD=hemodialysis

### 2.3 Prospective Switch Studies

The term “switch study” is used in this and the subsequent section. The term refers to studies that examine outcomes before and after conversion of a whole population from one ESA to the other (also referred to as historic control or pre- and post- study).

Hirai et al switched 104 Japanese hemodialysis patients who were stable on IV epoetin alfa to IV darbepoetin using the 200:1 ratio and followed them for 52 weeks to determine changes in hemoglobin and darbepoetin dose.<sup>24, 39</sup> Hemoglobin was measured every two weeks and darbepoetin doses were varied to maintain hemoglobin between 10-12g/dL. Intravenous iron supplementation was given to maintain TSAT above 20% and serum ferritin above 100ng/mL. There was no discussion of pre-defined dosing protocols. Initial results were published after 24 weeks of follow-up at which point they found the dose conversion ratio to be 1:350.5 (darbepoetin: epoetin). At 24 weeks 100 subjects remained in the study. After 52 weeks, 85 patients remained in the study and the final dose conversion ratio was found to be 1:286.6. The initial 1:200 conversion ratio led to a rapid increase in hemoglobin in the darbepoetin group, particularly in the first 8 weeks and the dose of darbepoetin subsequently decreased gradually until it stabilized at 20 weeks. The study population was divided into those with initial high and low doses of epoetin and diabetics and non-diabetics to determine if the findings would be different. Similar results were found in the diabetics and non-diabetics. Patients initially on higher doses of epoetin (>4500 units weekly) had a higher conversion ratio compared to those switching from lower doses. The authors concluded that darbepoetin may lead to reduced costs as compared to epoetin and that it may be more effective in resistant anemia because less was required in those on higher initial epoetin doses.

Nakagawa, in a letter to the editor,<sup>40</sup> describes switching 26 hemodialysis patients in Japan from epoetin alfa to darbepoetin using the 200:1 ratio. The goal was to maintain hemoglobin between 10-11g/dL with erythropoiesis stimulating agents and iron. "Cost-

effectiveness” is stated as the outcome measured and is defined as cost per unit (g/L) of hemoglobin. The final stable dose of darbepoetin was less than the dose at initiation in almost all patients with a savings of 34.1%. The total cost of epoetin alfa from the 32<sup>nd</sup> to 35<sup>th</sup> week of 2007 and the hemoglobin in the 34<sup>th</sup> and 36<sup>th</sup> week of 2007 were compared to the total cost of darbepoetin from the 2<sup>nd</sup> to the 5<sup>th</sup> week of 2008 along with the hemoglobin from the 4<sup>th</sup> and 6<sup>th</sup> week. It was determined that epoetin cost ¥3109/1g/dL of hemoglobin/patient and darbepoetin cost ¥2149/1g/dL of hemoglobin/patient. Of note, the route of administration was not specified in this letter and the study was very small with outcome measurements over very short time periods.

Bock, in 2007, designed a study to explicitly investigate the dose conversion ratio between epoetin and darbepoetin in Switzerland.<sup>25</sup> One hundred thirty two hemodialysis patients from 17 centres were enrolled and IV or SC epoetin alfa or beta was switched to IV darbepoetin using the 200:1 ratio. A study protocol was used for darbepoetin dosing in which hemoglobin was measured every two weeks and stepwise dose adjustments were made to maintain Hb within  $\pm 1$ g/dL of each subject’s baseline value (baseline 10.8-13g/dL). Intravenous iron was administered as per the protocols of each individual study centre to maintain TSAT above 20% and ferritin above 100 $\mu$ g/L. Dose titration and stabilization took place over 20 weeks followed by a 4 week evaluation period. The primary endpoint was the change of darbepoetin dose between baseline and the evaluation period required to maintain hemoglobin within 1g/dL of baseline value. Secondary endpoints included change in darbepoetin dose and change in mean hemoglobin and safety variables. One hundred patients completed the study and the mean final conversion

ratio was 1:336 (darbepoetin:epoetin) (95% CI 284-388). The mean darbepoetin dose at baseline was 34.7 $\mu$ g compared to 26 $\mu$ g during the evaluation period, with a continuous decrease in the darbepoetin dose throughout the course of the study that was most pronounced between weeks 5-9. A stepwise linear regression model of dose saving of darbepoetin versus baseline epoetin dose, route of administration, type of epoetin (alfa or beta) and dosing frequency found only baseline weekly epoetin dose to be significant after the elimination of all other variables with a curvilinear relationship between baseline epoetin dose and the conversion factor.

Icardi et al published a study in 2007 out of Italy in which 25 hemodialysis patients were switched from IV epoetin alfa to IV darbepoetin.<sup>26</sup> Dose adjustments of ESA were made in 25% increments when Hb fell outside of 10.5-12.5g/dL. Iron status was maintained with intravenous iron to maintain ferritin above 100ng/mL and TSAT above 20% as per a standardized dose protocol. Subjects were followed for 6 months on IV epoetin alfa (phase 1) then were switched using a 200:1 ratio and followed for a subsequent 12 months (phase 2). The epoetin:darbepoetin dose ratio was evaluated and pharmacoeconomic analysis was performed. In phase 1 the mean weekly epoetin dose showed no significant variation. In phase 2 the epoetin:darbepoetin conversion factor rose progressively from 200-256.1:1 at month 7 and 336.8:1 at month 12. The conversion translated into cost savings. This was a very small study and while 40 subjects consented, 15 were excluded after consent for various reasons. In addition, 4 of the 25 patients showed relative erythropoietin resistance but remained in the study.

Shalansky et al aimed to assess the efficacy of IV darbepoetin to maintain Hb compared to SC epoetin alfa in a Canadian study from 2003-2004.<sup>32</sup> This was an 18 month, open label observational study of 95 hemodialysis patients who were switched to darbepoetin as per the manufacturer's conversion table with some modifications (for available prefilled syringes and one dose category was divided into two narrower categories). At the time of the switch, data was collected retrospectively for 6 months and prospectively after the switch for 12 months, the first 6 months after the switch was a dose titration phase. ESA dose adjustments were made in 25% increments to maintain Hb between 120-135g/L. Iron was administered IV or orally to maintain TSAT 20-50% and serum ferritin 100-800µg/L. The primary outcome was to measure Hb to determine if darbepoetin was as effective in maintaining targets as epoetin. The secondary outcomes were to evaluate the manufacturer's recommended guidelines for conversion and to assess the cost implications of switching to darbepoetin. They found no significant difference in Hb between any of the study phases. The dose conversion ratio was calculated by comparing the mean weekly dose of epoetin at the time of the switch to the mean weekly dose of darbepoetin at each three-month interval in phase 2. Based on their results a dosing nomogram was developed in which all patients receiving 7000 units of epoetin weekly or less would be converted by the 200:1 ratio and those receiving greater than 7000 units weekly would use 300:1. A cost analysis was performed comparing mean darbepoetin usage over each time period to baseline epoetin dose, adjusted for patient numbers and assuming the baseline epoetin dose would have remained stable over 12 months, the median 12 month cost savings associated with darbepoetin was estimated at \$212 000. The authors state that the cost savings would have likely been higher if they

had been converting from IV epoetin as the IV route is associated with one-third higher epoetin dose requirements.

Roger et al published a study out of Australia in 2004 in which 60 hemodialysis patients were followed after switching from SC epoetin alfa to once weekly darbepoetin using a 200:1 ratio to review the dose requirements and cost of switching.<sup>27</sup> In phase 1 data was collected for 3 months before the switch and 3 months after the switch. In the second phase all patients were switched to double the darbepoetin dose every 2 weeks and were followed for 3 months. A protocol was used to adjust the dose of ESAs to maintain target Hb levels of 120-130g/L. An attempt to ensure adequate iron was made by aiming for a ferritin level between 300-600 $\mu$ g/L by administering IV iron weekly. Hemoglobin and ferritin remained within target during phase 1 but darbepoetin doses fell from 50.8 $\mu$ g to 42.3  $\mu$ g by the third month and the dose conversion ratio increased to 275.9:1. In phase 2, Hb was not maintained and doses had to be increased from 44.9 $\mu$ g to 47.5 $\mu$ g per week. They concluded that darbepoetin cost less per patient per year but the cost advantage is not as great when administered every two weeks to all patients.

Martinez et al conducted a single-arm, multicenter trial in Spain which assessed the maintenance of Hb concentrations between 10-13g/dL in 826 dialysis patients (94% hemodialysis, 6% peritoneal dialysis) after switching from epoetin to darbepoetin.<sup>41</sup> The study was published in 2003 and included both IV and SC administration of both epoetin and darbepoetin. Subjects were switched to darbepoetin using a 200:1 ratio and were followed for 24 weeks – a 20 week titration period followed by a 4 week evaluation

period. The study was completed by 86.8% of subjects and they found no significant change in Hb with a mean reduction of 9.8% in the darbepoetin IV dose and 4.7% in the darbepoetin SC dose.

Locatelli et al conducted a multi centre study in 19 European centres which was published in 2003.<sup>36</sup> Three hundred forty one dialysis patients (329 hemodialysis, 14 peritoneal dialysis) on IV or SC epoetin alfa or beta were switched to IV or SC (maintaining same route) darbepoetin using a 200:1 ratio. There were 76 subjects receiving IV and 267 receiving SC administration. Darbepoetin doses were adjusted to maintain each patient's hemoglobin within a target range of -1.0 to +1.5g/dL of the mean baseline hemoglobin and between 10-13g/dL throughout the study period. A dose protocol was used in which the dose was increased or decreased stepwise if the Hb was out of range for two consecutive assessments. Iron was administered intravenously as per individual unit policy to maintain serum ferritin above 100µg/L. The primary outcome was the change in Hb from baseline to weeks 21-24 post conversion and the secondary outcome was the dose and frequency of darbepoetin administered. They found no difference in mean change in Hb. There was a significant decrease of 15% in the mean weekly IV darbepoetin dose from baseline to the evaluation period (25.2 µg to 21.5 µg) and the SC dosing requirement increased slightly from 20.8 µg to 22.7 µg weekly. They determined that the increase SC requirement seen was due to patients being sub-optimally managed on SC epoetin before the switch.

Martin-Holohan published a small pilot study of 14 hemodialysis patients in the United States in which hemodialysis patients were switched from SC epoetin alfa to SC darbepoetin.<sup>33</sup> Subjects were switched using the manufacturer's conversion chart and were followed for 4 months to evaluate efficacy as measured by Hb levels and cost. Dose adjustments were made to maintain Hb levels between 110-120g/L, if Hb was below target the dose was increased by 50% and if above target the dose was decreased by 25%. Of the 12 patients who completed the study, 4 were not within Hb range before the switch and all of these required dose increases. In the other 8, half required one or more dose increases to maintain target. The cost analysis revealed that darbepoetin cost more but the difference was not statistically significant. This study was very small and not well designed in that one third of the patients were not at target at the time of switch. The dosing protocol with 50% increases was also unusual in that most dosing protocols use 10-25% dose changes. The authors claim that they demonstrated that the manufacturer's conversion table resulted in insufficient darbepoetin doses, but it would be difficult to make any firm conclusions from this study.

The nine prospective switch studies are summarized in Table 3. While none of these studies were ideally designed to answer the research question, four demonstrated a dose conversion ratio (epoetin:darbepoetin) which was greater than 200:1, four found decreased doses and lower cost with darbepoetin compared to epoetin and one found darbepoetin cost more than epoetin but the result was not statistically significant.

**Table 3: Prospective Switch Studies**

	Subjects	ESA	Targets (Hb, Fe) Follow-up	Outcomes	Results
Hirai Japan, 2009-2010	HD n=104	IV epoetin $\alpha$ to IV darbepoetin	Hb 100-120g/L TSAT>20% Ferritin >100ng/mL.  24 weeks and 52 weeks	Change in Hb and Darbepoetin dose	- Dose conversion ratio at 24 weeks 1:350.5 - Dose conversion ratio at 52 weeks 1:286.6
Nakagawa Japan, 2007 (letter to the editor)	HD n=26	epoetin $\alpha$ to darbepoetin ( route not specified)	Hb 10-11g/dL  Compared 2 four week periods	Cost effectiveness (cost per 1g/dL Hb per patient)	- epoetin cost ¥3109/1g/dL of Hb/patient - darbepoetin cost ¥2149/1g/dL of Hb/patient - savings of 34% with darbepoetin
Boek Switzerland, 2007	HD n=132	IV or SC epoetin $\alpha$ or $\beta$ to IV darbepoetin	Hb within 1g/dL of baseline (baseline 10.8-13g/dL) TSAT>20% Ferritin>100 $\mu$ g/L.  24 weeks	1 <sup>o</sup> -change of darbepoetin dose  2 <sup>o</sup> -change in mean Hb and safety variables	- mean final dose conversion ratio 1:336 - curvilinear relationship between baseline epoetin dose and darbepoetin dose
Icardi Italy, 2007	HD n=25	IV epoetin $\alpha$ to IV darbepoetin	Hb 10.5-12.5g/dL Ferritin >100ng/mL. TSAT>20%  12 months	Dose conversion ratio	- at month 7 ratio 256.1:1 - at month 12 ratio 336.8:1
Shalansky Canada, 2005	HD n=95	SC epoetin $\alpha$ to IV darbepoetin	Hb 120-135g/L. TSAT 20-50% Ferritin 100-800 $\mu$ g/L.  18 months	1 <sup>o</sup> -efficacy of darbepoetin compared to epoetin  2 <sup>o</sup> -evaluate recommended conversion guidelines. assess cost	- no significant difference in Hb - median 12 month cost savings \$212 000 with darbepoetin - suggest converting epoetin 7000units weekly or less using 200:1 & greater than 7000 units using 300:1
Roger Australia,2004	HD n=60	SC epoetin $\alpha$ to IV darbepoetin	Hb 120-130g/L Ferritin 300-600 $\mu$ g/L.  6 months	Dose requirements and cost of switching	- darbepoetin doses fell and dose conversion ratio rose to 275.9:1
Martinez Castelao Spain, 2003	HD(94%) & PD n=826	IV and SC epoetin to IV and SC darbepoetin	Hb 10-13g/dL  24 weeks	Maintenance of Hb and dose required	- no change in Hb - 9.8% reduction in IV darbepoetin dose - 4.7% reduction in SC darbepoetin dose
Locatelli Italy, 2003	HD & PD n=341	IV or SC epoetin $\alpha$ or $\beta$ to Darbepoetin	Hb 10-13g/dL. Ferritin>100 $\mu$ g/L.  24 weeks	1 <sup>o</sup> - change in Hb 2 <sup>o</sup> -dose and frequency of darbepoetin	- No change in Hb - Decrease of 15% in mean IV darbepoetin dose from baseline - Small increase in SC darbepoetin dose required
Martin-Holohan US, 2004	HD n=12	SC epoetin $\alpha$ to SC darbepoetin	Hb 110-120g/L  4 months	Hb and cost	- 4/12 required dose increases to meet target Hb - Cost analysis: darbepoetin cost more but not statistically significant

HD=hemodialysis, PD=peritoneal dialysis

#### 2.4 Retrospective Switch Studies

Sharma et al conducted a retrospective observational cohort study in the United States from 2004-2005 with the goal of determining a robust empirical method to assess the dose conversion ratio between epoetin and darbepoetin.<sup>28</sup> Data was collected from the charts of hemodialysis patients from 25 hospital-based units who were switched from IV epoetin alfa to IV darbepoetin alfa. Twenty six randomly selected charts were chosen from each centre to provide data from 337 patients. Two analysis time frames were chosen of 8 weeks each – weeks 2-9 before conversion to darbepoetin and weeks 21-28 after conversion, with 20 weeks in between to prevent carryover effects. Mean maintenance dose conversion ratios were calculated by two methods, one regression-based (ordinary least squares) and the other ratio-based (arithmetic mean). Hemoglobin levels were comparable in both time frames. The regression based method provided a dose conversion ratio of 320:1 and the ratio-based method 350:1, with sensitivity analyses yielding ratios from 311-333:1. The paper did not discuss if dosing protocols were in place in the centers under study for ESA or iron.

Agrawal examined a retrospective cohort of 98 hemodialysis patients in the United States in a single centre who were switched from IV epoetin alfa to IV darbepoetin between 2005 and 2006 using the manufacturer's conversion chart as part of a therapeutic interchange program.<sup>42</sup> The goal was to compare the effectiveness of the two ESAs by comparing mean Hb and variability. Data was collected for 8 months before the switch while still on epoetin, during the four month titration phase after the switch to darbepoetin and then for nine subsequent months. ESA doses were adjusted monthly to maintain the

individual's Hb between -1.0 and +1.5 g/dL of their baseline values with an overall target Hb of 11-13g/dL. If two consecutive assessments yielded Hb outside the target range, then doses were changed by 25%. Intravenous iron was used to maintain ferritin above 200ng/mL and TSAT above 20%. The mean Hb levels, the proportion of patients able to achieve target Hb, and the Hb variability were not different between the two groups. The median dose of darbepoetin required to maintain Hb targets in the final 9 month phase increased significantly compared with baseline demonstrating a dose conversion ratio of 190.8:1.

Raymond et al performed a retrospective chart review of a switch from epoetin alfa to darbepoetin in hemodialysis, peritoneal dialysis and chronic kidney disease patients between 2003 and 2005 to determine dose conversion ratios.<sup>29</sup> In 2004 in Manitoba, a policy change brought about this switch in ESAs based on a pilot study that demonstrated a dose conversion ratio >200:1. Patients on both IV and SC epoetin were switched to the same route darbepoetin using the manufacturer's recommendations. Darbepoetin doses were titrated to a target Hb of 110-120g/L and iron was administered to maintain ferritin of 100-800ng/L and TSAT 20-50%. The study compared 857 patients on darbepoetin in 2005 (June to August) with 746 patients on epoetin in 2003-2004 (3 months of data). The mean dose conversion ratios for IV administration in hemodialysis patients was 244:1, for SC administration in peritoneal dialysis patients was 222:1 and for SC administration in chronic kidney disease patients was 219:1.

Biggar et al conducted a retrospective cohort study of 90 hemodialysis patients as a quality control initiative to describe dose conversion ratios after a dialysis centre in Germany underwent a switch from darbepoetin alfa to epoetin beta using a 200:1 ratio.<sup>30</sup> Dosing of ESA followed the “usual clinical routine” to maintain Hb targets of 11-12g/dL and iron status was maintained with intravenous iron to keep TSAT between 20-30%. The study collected data from 12 weeks before the switch and 16 weeks after the switch to analyze ESA dose and Hb level. After the switch to epoetin the mean Hb level decreased significantly from 11.4g/dL to 11.1g/dL. The mean ESA dose required increased by 13% in the overall evaluation period. In the last four weeks the dose increased by 17%, suggesting a conversion ratio of >233:1.

Brophy et al in the United States conducted a retrospective chart review following a therapeutic interchange program which switched all hospitalized hemodialysis patients from epoetin alfa to darbepoetin.<sup>35</sup> They compared drug expenditures over a fiscal quarter in 2003 in 86 patients before the switch with historical comparator data from 56 patients in 2002. Data was also collected on patient demographics, drug utilization, and change in Hb for comparison purposes. The route of administration of the ESAs was not specified in the paper. There was no dosing protocol in place for epoetin but there was for darbepoetin after the switch. Patient demographics were similar between groups. Nearly all of the patients evaluated in the epoetin group were on drug, as no dosing protocol was in place. Comparatively, there was significantly less drug used in the darbepoetin group, only one-third of the patients received darbepoetin. The economic analysis demonstrated cost savings and reduced drug utilization with nearly \$10 000 saved in the first quarter,

however this could be explained by the dosing protocol being implemented and not necessarily by the choice of ESA. Although it is worth noting that the cost per patient treated was lower with darbepoetin than epoetin. This study was in hospitalized patients only so it has limited generalizability.

Sterner, in a letter to the editor, describes a retrospective analysis of a switch from SC epoetin beta to IV or SC darbepoetin in 155 hemodialysis patients in Sweden.<sup>31</sup> Data was collected for an 8 month period after the switch and Hb levels and ESA doses were evaluated. It is not clear if a dosing protocol was used, but it is stated that iron administration was kept at an optimal level. The mean Hb at the start was 120g/L and it was 119g/L after 8 months. The mean epoetin beta weekly dose was 10 730 units and the mean weekly darbepoetin dose was 48.1µg giving a mean conversion ratio of 257:1.

The retrospective switch studies are summarized in Table 4. Of the six studies reviewed, four found the dose conversion ratio (epoetin:darbepoetin) to be greater than 200:1, one found the dose conversion ratio to be less than 200:1 and one found cost savings and reduced drug utilization with darbepoetin compared to epoetin. Again, these studies were not designed to specifically answer the research question of interest and would also have the added inherent biases and limitations of retrospective studies.

**Table 4: Retrospective Switch Studies**

	Subjects	ESA	Targets (Hb, Fe) Follow-up	Outcomes	Results
Sharma US, 2010	HD n=337	IV epoetin $\alpha$ to IV darbepoetin	Not reported  8 weeks before and 8 weeks after	To determine dose conversion ratios	- 320:1 (regression based method) - 350:1 (ratio based method)
Agrawal US, 2009	HD n=98	IV epoetin $\alpha$ to IV darbepoetin	Hb 110-130g/L Ferritin >200 $\mu$ g/L TSAT >20%  8 months before, 4 months titration, 9 months evaluation	To determine dose conversion ratio	- 190.8:1
Raymond Canada, 2008	HD, PD, CKD n=1603	IV or SC epoetin $\alpha$ to IV or SC darbepoetin	Hb 110-120g/L Ferritin 100-800ng/L TSAT 20-50%  3 months before and 3 months after	To determine dose conversion ratios	- HD: 244:1 (IV) - PD: 222:1 (SC) - CKD: 219:1 (SC)
Biggar Germany, 2008	HD n=90	IV darbepoetin to IV epoetin $\beta$	Hb 110-120g/L TSAT 20-30%  12 weeks before and 16 weeks after	ESA dose and Hb	- Mean epoetin dose increased by 13% - Suggest conversion ratio of >233:1 - Hb decreased significantly after switch
Brophy US, 2005	HD- hospitalized n=142	Epoetin alfa to darbepoetin (route not reported)	Not reported  3 months before and 3 months after	Drug utilization and cost, change in Hb from admission to discharge	- Resulted in cost savings and reduced drug utilization - The average cost per patient treated was lower with darbepoetin than epoetin - No change in Hb
Sterner Sweden, 2008 (letter to the editor)	HD n=155	SC epoetin $\beta$ to IV or SC darbepoetin	Not reported  8 months after switch	Hb and ESA dose	- Hb stable - Mean dose conversion ratio was 257:1

HD=hemodialysis, PD=peritoneal dialysis, CKD=Chronic Kidney Disease

## 2.5 Cross-Sectional Studies

Courtney published a cross-sectional analysis of ESA prescribing from four dialysis centres in Northern Ireland in 2006.<sup>43</sup> The four units shared the same guidelines for ESA and iron dosing, although the choice of agent and route of administration were at the discretion of the individual nephrologist. Data was collected on 403 patients including 184 on epoetin beta and 219 on darbepoetin to compare mean Hb between groups and

ESA dosing. Over a selected one week period the ESA, dose, route of administration, iron dose, Hb, ferritin, TSAT, and PTH were collected. Patients could be on either SC or IV ESA. The mean Hb was comparable between groups. They determined the dose conversion ratios to be 176:1 between SC epoetin and SC darbepoetin, 200:1 between IV epoetin and IV darbepoetin and 173:1 between SC epoetin and IV darbepoetin. Based on this, SC epoetin beta was the most cost effective ESA in this population.

## 2.6 Economic Studies

Churchill, in 2007, published a prospective observational study of non-acquisition costs associated with ESA administration with the goal of determining how much costs could be decreased with the less frequent dosing of darbepoetin and less frequent ferritin monitoring.<sup>44</sup> The costs associated with anemia management were evaluated in 450 hemodialysis patients in Hamilton in 2001 who were receiving SC epoetin alfa with a target Hb of 110-120g/L and IV iron to maintain ferritin above 100µg/L and TSAT above 20%. These data were used to estimate costs in 2005 using an inflation factor. Time-and-motion technique was used to determine nursing time for preparation and administration. Fixed anemia costs included inventory control, monitoring, blood sampling and lab analysis. Variable costs were those that varied with dosing frequency. A dose conversion ratio of 200:1 and dosing every 2 weeks was assumed for darbepoetin. The analysis found that less frequent iron monitoring and less frequent ESA dosing would decrease costs by \$678.40 and \$199.38 per patient year respectively. More specifically, in changing from three times weekly epoetin to once weekly darbepoetin \$308.11 per year per patient

would be saved and from twice weekly epoetin to once weekly darbepoetin \$154.05 per year per patient. It was noted that the change in iron monitoring would represent a monetary cost reduction whereas the decreased dosing represents nursing time which would not likely lead to a decrease in nursing staff. As is standard in economic analyses, the time represents a potential cost savings in the long run assuming that resources can be deployed differently and more efficiently.

Morreale conducted a cost-minimization analysis in the United States in 2003 to compare epoetin alfa and darbepoetin.<sup>45</sup> The goal was to calculate a cost ratio based on the available clinical trials in both chronic kidney disease and oncology. As comparative head to head trials were not available, they claimed that clinical endpoints in the available studies were similar and used them to conduct the analysis from a provider's perspective. Using data from the selected studies they calculated cost comparison ratios of darbepoetin:epoetin in the different patient populations and concluded that epoetin alfa is a better pharmacoeconomic value overall. In dialysis the cost ratio was 1.5 and 2 in the two studies used. Specifically in hemodialysis a cost ratio of 1.4-3 was found in the one study used. This economic analysis was based on a limited number of studies and costs were determined based on available vial sizes at the time. The results would be of questionable relevance currently.

Kruep et al conducted a cost-minimization analysis to compare darbepoetin and epoetin alfa in the hospital wide setting.<sup>34</sup> It was an observational retrospective review of use for all indications in the United States in 2003. They considered total costs including drug

product costs and administration costs. There were 429 records of epoetin and 80 records of darbepoetin and data was collected to determine the dose conversion ratio. The overall dose conversion ratio based on median daily dose of each drug was found to be 245:1, the authors concluded that there was no cost difference between the two as they determined the breakeven point to be 239:1. Sensitivity analyses were conducted and found that a cost benefit would only be realized when the dose conversion ratio exceeded 257:1. This study may have limited applicability as it was in the hospital setting only, it included ESA use for all indications and there were many assumptions made about drug vial size (i.e. for a 5000 unit dose, a 10 000 unit vial was assumed to be used).

## 2.7 Systematic Reviews

Cremieux published a systematic review based on comparative switch and non-switch studies in CKD published between 2000 and 2005.<sup>46</sup> A dose ratio from epoetin alfa to darbepoetin was calculated for each study and the results were stratified by study characteristics. Multivariate regression analysis was used to control for differences in study design and a dose conversion ratio for Canada was estimated. They identified 21 studies involving 16 378 patients from the United States, Canada, Europe and Australia. There were 15 switch studies, 4 randomized controlled trials and 2 parallel group studies with an average treatment period of 26.4 weeks. Univariate analysis of the dose ratios gave a mean dose ratio of 217:1 and multivariate analysis demonstrated that the study design and the geographical area affected the results. Based on the multivariate analysis the dose conversion ratio for Canada was determined to be 169:1, meaning epoetin alfa would cost 11-18% less than darbepoetin. There was much variation in design amongst

the small number of studies used with a lack of uniformity in the outcomes measured and a likely variation in iron status (this was not managed in the analysis as most did not report information on iron supplementation). As most were switch studies, they would have the bias inherent in this type of study (discussed in Summary). Also there was insufficient data to conduct a systematic analysis of the change in dose conversion ratio over time and there is evidence to suggest that the ratio changes over time as the darbepoetin dose stabilizes.

Duh conducted a systematic review in 2008 in which the pharmacoeconomic evidence on the comparative cost effectiveness of epoetin alfa, epoetin beta and darbepoetin in CKD, oncology and other disease areas was reviewed.<sup>14</sup> Studies published between 2000 and 2007 were used and in the dialysis population there were 4 studies identified. In the end the authors state that it is difficult to draw conclusions about the relative cost effectiveness in this population from the literature that is available, even though a number of studies suggest an advantage for epoetin alfa. It is noted that cost differences exist between countries making comparisons difficult – in Canadian studies, hospital contract prices are often used whereas in US studies wholesale costs are more common. The majority of the studies reviewed in this paper are from the oncology literature.

A systematic review and economic evaluation of ESAs in CKD was published by CADTH (Canadian Agency for Drugs and Technology in Health) in 2008.<sup>37</sup> This review was done primarily to address the uncertainty about using ESAs to target higher Hb levels. Randomized controlled trials in anemic adults with CKD managed with epoetin,

darbepoetin or without ESA were included to conduct a cost-utility analysis from the perspective of the Canadian public health care system using a lifetime horizon. Base case analysis and probabilistic sensitivity analyses were done. The results showed that intermediate and low Hb targets are optimal and that a Hb target of 110g/L produces the largest number of quality adjusted life years (QALYs) at an additional cost per patient lifetime. However, this was based on the assumption that the intermediate target will improve quality of life compared to the low Hb target and this is unproven. In dialysis specifically, they found costs could be reduced if SC epoetin or darbepoetin (IV or SC) were used instead of IV epoetin. The authors state that head-to-head comparisons of epoetin and darbepoetin should be undertaken because even small differences in potency per unit cost of ESA can translate into large difference in total costs to the Canadian public health care system.

## 2.8 Summary

The one randomized controlled trial with just intravenous ESA administration did not have dose or cost as the primary outcome. The other two which did evaluate dose involved subcutaneous administration. The route of administration is very important as ESAs in hemodialysis patients are almost exclusively administered by the intravenous route.

The term “switch study” is being used for studies that examine outcomes before and after conversion of a whole population from one ESA to the other (also referred to as historic control or pre- and post- study). In such studies it is difficult to interpret and generalize

results due to the absence of a control group and the tendency for ESA requirements to change in hemodialysis populations over time as guidelines and practices evolve.

Particularly in the retrospective switch studies, the cohorts compared were often different groups of patients over different time periods, this alone could account for a difference in ESA requirement.

Most of the prospective switch studies did not include a pre-switch component in which the epoetin doses were stabilized. Without this, there is the potential that epoetin dosing before the switch may have been sub-optimal or patients may not have been iron replete. Once the switch to darbepoetin occurred many of the studies describe set dosing protocols or iron and hemoglobin targets. Any differences found could have been in part due to more diligent dosing post switch. Of the prospective switch studies, only two were in North America, several had a follow up period of less than 6 months and not all used standard, pre-defined dosing protocols.

In the retrospective switch studies there is the added limitation of potential selection bias, several compared completely different groups of patients from different time periods, only two of the six evaluated longer than 6 months post-switch, most did not identify set protocols for dosing ESA and iron, and many did not report if subjects were iron replete. Some of the authors of these papers suggest that retrospective cohort studies may be more generalizable and representative of the real-world dialysis population than a prospective study which excludes many patients for a variety of reasons. While generalizability may be limited in prospective studies and trials with inclusion criteria, the potential for bias in

the retrospective studies remains and would limit the conclusions and inferences that could be drawn from the results.

The cross-sectional study examined a one week period only in four different centres in Ireland without standardized dosing protocols. It may have use in describing practice patterns in this region at a given time, but could not be relied upon to make conclusions about cost differences of ESAs for all dialysis patients.

Of the three economic analyses, one focused on non-acquisition costs only, one combined CKD and oncology trials and the third was just in the inpatient hospital setting. These were based on a limited number of studies, mostly observational switch studies with a variety of designs and a number of limitations. The most applicable systematic review to address the question was done in Canada but even here the authors concluded that more head-to-head comparisons are needed to fully evaluate any cost differences between epoetin and darbepoetin.

None of the studies identified met all the desired characteristics to address the question of a cost advantage for intravenous epoetin or darbepoetin in the management of CKD anemia in hemodialysis patients. Overall, the results of the various study types demonstrated a trend towards lower dose requirements with darbepoetin and higher dose conversion ratios than 200:1.

## Chapter 3 Research Design

### 3.1 Overview

This study was an open label, unblinded, randomized controlled trial of intravenous darbepoetin alfa (Aranesp®) versus epoetin alfa (Eprex®). Eligible subjects were prevalent and incident hemodialysis patients who were unlikely to recover renal function, required ESA therapy, did not have a known cause for anemia other than chronic kidney disease, and did not meet the criteria for ESA resistance. Subjects were enrolled over a minimum six week run-in period to ensure that the hemoglobin was stable within the target range. The active study period then continued for a subsequent 12 months. ESA and iron were dosed according to an algorithm designed to maintain hemoglobin within the currently recommended target range of 100-120g/L. Subjects could be recruited from any of the following dialysis units: Health Sciences Center Dialysis Unit (St. John's, NL), Waterford Hospital Dialysis Unit (St. John's, NL) or Carbonear Dialysis Unit (Satellite Unit, Carbonear, NL).

### 3.2 Outcomes

The primary outcome was the cost per patient of ESA required to maintain hemoglobin in the target range over 12 months. Secondary outcomes included time to dose stabilization, number of dose changes, the dose conversion ratio, iron dose and cost and deviation from target ranges for hemoglobin and iron indices.

### 3.3 Sample Size Calculation

Because the primary outcome was cost, any of several statistical approaches to sample size calculation were appropriate. An important assumption of this study was that the clinical effectiveness and hence the clinical utility of both treatments is identical.

Because of this, a cost minimization analysis was done and more complicated approaches to sample size calculation for economic analyses that allow the cost and the clinical benefit of each treatment to vary were not required.

The primary analysis was a comparison of cost per patient per year between groups. An audit of the dialysis unit in St. John's determined that the mean direct drug cost per patient over 12 months was approximately \$7,000 with a standard deviation of \$1,500 (not inclusive of pharmacy and nursing costs). Based on these figures, the total number of patients required to detect a difference of \$800 per patient with 2-sided  $\alpha=0.05$  and power  $(1-\beta)=0.80$  was 112, or 56 per group.

### 3.4 Subjects

The eligible study population included patients receiving or initiating hemodialysis who met the following **inclusion criteria**:

1. Age  $\geq 19$  years

2. End-stage chronic kidney disease necessitating maintenance hemodialysis therapy that, in the opinion of the responsible physician, was permanent and unlikely to resolve with or without treatment
3. Receiving hemodialysis two or more times weekly
4. Anemia due to renal failure requiring ESA therapy OR a Hb < 100g/L in the absence of other causes of anemia
5. If female, must be using an approved method of contraception (barrier, hormonal contraceptives) or judged unable to become pregnant
6. Able to understand and sign the informed consent document

Patients who met any of the following **exclusion criteria** were not eligible for study participation:

1. Renal failure that, in the opinion of the responsible physician, was acute and likely to resolve
2. Being treated with, or definite plans to change to, peritoneal dialysis (PD), home hemodialysis, home nocturnal dialysis or planned transplant from a living donor
3. Presence of a medical condition other than renal failure expected to limit the patient's lifespan to less than six months from the time of assessment
4. Current diagnosis of a hematologic condition other than erythropoietin and / or iron deficiency that may cause anemia
5. Current use of medications known to cause anemia
6. Use of any investigational drug or androgens within 90 days of screening

7. Documented significant bleeding, including gastrointestinal bleeding, pulmonary hemorrhage, gross hematuria or menorrhagia, that was either untreated or unresolved, within 30 days of screening
8. Red blood cell transfusion(s) within 30 days of screening
9. Documented or suspected pure red cell aplasia (PRCA)
10. Current iron deficiency (i.e. ferritin  $< 200\mu\text{g/L}$  and / or transferrin saturation  $< 20\%$ ). Patients were eligible for enrollment if this was subsequently corrected using intravenous iron therapy
11. Documented allergy or intolerance to intravenous sodium ferric gluconate (Ferrlecit®)
12. Known or probable ESA resistance. For the purpose of this study, resistance was defined as:
  - a. a current requirement for Eprex ®  $\geq 250$  units/kg/week
  - b. documented current vitamin B12 and / or folate deficiency
  - c. the presence of an untreated or unresolved malignancy, other than basal cell carcinoma
  - d. current iPTH (parathyroid hormone)  $> 1000\text{ng/L}$
  - e. the presence of an active infection (i.e. any infection that was currently being treated with antibiotics), any diagnosed infection that was not treated with antibiotics but have been awaiting therapy by other means (i.e. amputation of a gangrenous limb), or a history of osteomyelitis in the preceding 3 months even if antibiotic therapy has been completed

13. Uncontrolled hypertension (as determined by the attending nephrologist)
14. Inability to comprehend or unwillingness to sign the informed consent document
15. An intention to move away from the current region in the near future necessitating a change of dialysis center

### 3.5 Randomization

Eligible patients who agreed to participate in the study and signed the informed consent document were randomized prior to the run-in period using a variable, block randomization procedure. Before any subjects were enrolled, a random number sequence was used to determine the order of the variable blocks of 4, 6 or 8 and the sequence of assignment within each block. One of the investigators filled and numbered the opaque envelopes and the sequence was sealed and filed until the end of enrollment to ensure that the investigators were blinded to the order of assignment. As each subject was enrolled, a sealed envelope was sequentially opened by an investigator to assign the study subjects to one of two groups:

Group 1: Continued treatment with epoetin (Eprex ®) to maintain Hb 100-120 g/L

Group 2: Switch to darbepoetin (Aranesp ®) to maintain Hb 100-120 g/L

### 3.6 Study Protocol

#### 3.6.1 Run-In Period

The purpose of the run-in period was to ensure that subjects assigned to epoetin had a Hb that was stable in the 100-120g/L range, and to allow ESA conversion and dose titration of subjects in the darbepoetin group such that their Hb remained within an identical target range. Data from the run-in period was not included in the final analysis of drug cost, but Hb stability and time to target Hb were examined as secondary outcomes.

For both groups the run-in period was a minimum of six weeks. Hemoglobin levels were determined at mandatory two week intervals during the run-in phase. If an enrolled subject's hemoglobin was within the range of 100-120 g/L for three consecutive two-weekly measurements, that subject was considered stable and entered the active study phase. If a subject's hemoglobin deviated from the target range, drug dose adjustments were made according to the study algorithms (Appendices A and B) and the run-in period was extended until the stability criterion was met.

#### 3.6.2 Intervention

All changes in ESA and iron therapy were made in accordance with the specified study algorithms (Appendices A and B). Once a subject was enrolled in the study, all ESA and iron prescription adjustments were made by the study investigators. Hb was measured at baseline and every 2 weeks during the run-in phase. The second Hb measurement during the run in phase was used to ensure that Hb remained in a safe and acceptable range. If the Hb measure exceeded specified safety criteria the treating physician was alerted to

manage as they deemed appropriate. Such management could have included, but was not limited to, changes in the ESA dose, blood transfusion, further investigations or diagnostic tests. During the active study phase, Hb was measured monthly and dose changes were made as per the study algorithms.

### 3.6.3 Epoetin (Eprex®) Dosing

Patients who were enrolled and randomized to the epoetin group remained on their current dose and frequency for the first two week interval. After the first Hb measurement the study algorithm was used to guide anemia management (Appendix A). The first Hb measurement (at two weeks) was reviewed by the investigators to determine whether changes in epoetin were required to ensure patient safety or whether further investigations were required (see above). The second Hb measurement (at 4 weeks) was used to make changes in epoetin dose, if required, to maintain the patient's Hb in the target range. This cycle repeated itself throughout the run-in phase. During the active study phase, the Hb measurement was reviewed once monthly by investigators to determine if changes in epoetin dose were required to maintain the patient's Hb in the target range. This continued until the study terminated or the patient was withdrawn from the study.

If a subject required a dose of epoetin > 30 000 units weekly, the dose was not escalated any higher. Such a patient would likely meet the criteria for study withdrawal (see 3.9).

All epoetin was administered intravenously during dialysis through a hemodialysis machine port using a manufacturer-provided pre-filled syringe. This was the standard practice in the dialysis units.

#### 3.6.4 Darbepoetin (Aranesp®) Dosing

In patients who were randomized to the darbepoetin group, their current ESA was discontinued at the end of the week preceding entry into the study. These patients were switched to darbepoetin on the date that they would normally have received their next dose of ESA. Switching patients to darbepoetin was done using the conversion ratio of 200 units of epoetin to 1 µg of darbepoetin as used per week, rounded up or down to the nearest available pre-filled syringe dose available from the manufacturer. All darbepoetin was administered intravenously during dialysis through a hemodialysis machine port.

As in the comparator group, after the first Hb measurement the study algorithm was used to guide anemia management (Appendix A). The first Hb measurement (at two weeks) was reviewed by the investigators to determine whether changes in darbepoetin or other interventions were required. Because this group was undergoing a switch in their therapy, the potential existed for a significant change in Hb in either direction during the run-in phase. The protocol allowed the result of the first Hb measurement to be used to change the dose of darbepoetin if the subject's Hb fell out of range or if the investigator anticipated that this would occur without a change in dose. The second Hb measurement (at 4 weeks) was used to make changes in darbepoetin dose, if required, to maintain the patient's Hb in the target range. This cycle repeated itself throughout the run-in phase.

During the active study phase, the Hb measurement was reviewed once monthly by investigators to determine if changes in darbepoetin dose were required to maintain the patient's Hb in the target range. This continued until the study terminated or the patient was withdrawn from the study.

If a subject required a dose of darbepoetin  $>150\mu\text{g}$  weekly, the dose was not escalated any higher. Such a patient would likely meet the criteria for study withdrawal (see 3.9).

### 3.6.5 Iron Dosing

Iron supplementation is an integral component of anemia management in hemodialysis patients. The current practice of the participating dialysis units was to administer intravenous iron to patients as required to maintain serum iron indices within recommended ranges. There are three iron products available for use in Canada: iron dextran (Infufer®), Iron sucrose (Venofer®), and Sodium Ferric Gluconate (Ferrlecit®). All three formulations are used in the participating dialysis units and are considered equally efficacious.

Patients enrolled in this study received only one formulation of iron, Sodium Ferric Gluconate (Ferrlecit®), as it is moderate in cost and the risk of anaphylactoid reactions is significantly less than seen with iron dextran. The use of one iron product in all patients ensured a standard approach and eliminated a potential confounder.

Intravenous iron was prescribed if indicated according to the study algorithm (Appendix B) to maintain serum ferritin in the range of 200-800ng/mL and TSAT between 20-50%. As part of standard clinical practice, TSAT was measured monthly and ferritin every 3 months. The most recent values were used to determine study eligibility. After enrollment in the study, iron parameters continued to be measured at this frequency.

### 3.7 Data Collection and Storage

Data was obtained from the Meditech® system and / or the subject's chart as it was available at baseline and every two weeks thereafter during the run-in and once monthly during the active phase. Data was entered directly into a statistical software database (SPSS®) using unique patient identifiers that were not traceable to individual subjects by anyone other than the study investigators. All data was secured and stored in locked areas inaccessible to non-study personnel.

### 3.8 Analysis

Analysis of the primary outcome was a comparison of the total ESA cost over 12 months per patient in each group. The cost used in the analysis was the drug acquisition cost only (manufacturer's list price, Canadian dollars). The agents are priced such that the cost is equivalent for the two at a 200:1 dosing ratio (epoetin: darbepoetin). After determining that the distribution of the costs was not normal, medians and interquartile ranges were calculated and the medians were compared using the Mann-Whitney U test.

Secondary analyses included:

- A comparison of iron dose and cost over 12 months for each group
- A comparison of the achieved targets of anemia management between the two groups including Hb, TSAT and Serum Ferritin
- A comparison of the number of weeks and dose changes required to achieve dose stabilization in each group in the run-in phase
- A comparison of the number of dose changes throughout the active phase
- A calculation of the dose conversion ratio between epoetin and darbepoetin by comparing the epoetin dose prior to conversion with the darbepoetin dose at the point of dose stabilization and at the 3 and 6 month points of the active phase

For the secondary analyses, when the distribution of the data was normal, results were reported as means  $\pm$  standard deviation (SD) and the independent samples t-test was used to compare means. When the data was not normally distributed, results were reported as medians and interquartile range (IQR) and the nonparametric Mann-Whitney U test was used to compare medians.

### 3.9 Withdrawals

Patients who withdrew from the study prior to the active study phase were not included in the final analysis. Patients who withdrew from the study after this point were included in

the final intention to treat analysis, using all data that was available up until the point that the subject finished.

If patients had required blood transfusions, they would not have been withdrawn from the study for this reason alone. The data from these patients would have been included in the final analysis, but the occurrence and frequency of transfusions would have been noted in the final results. In the circumstance that a subject previously requiring ESA no longer required it to stay in the target Hb range, that patient was not withdrawn from the study.

At any point an individual patient may develop a condition that significantly alters their response to ESA or, at the extreme, makes the use of ESA futile or impractical. A patient who is diagnosed with a malignancy, for example, may undergo chemotherapy that will cause severe anemia. Withdrawals from the study protocol were permitted at the investigator's discretion for the following reasons:

1. newly documented or suspected pure red cell aplasia (PRCA)
2. a newly diagnosed hematologic condition other than erythropoietin and/or iron deficiency that may cause anemia and was not immediately remediable
3. the initiation of drug therapy that was expected to cause anemia or significantly impact the patient's response to ESA, e.g. chemotherapy
4. the diagnosis of significant bleeding, including gastrointestinal bleeding, pulmonary hemorrhage, gross hematuria or menorrhagia, that was either untreatable or not to be treated
5. withdrawal of renal replacement therapy

6. clear evidence of ESA resistance, regardless of cause, such that the attending physician determined that it would be futile to further increase the dose of ESA

### 3.10 Ethical Considerations

Ethics approval was obtained for this study from the Health Research Ethics Authority (HREA, formerly the HIC – Human Investigation Committee) in July 2010, with subsequent renewals in 2011 and 2012. The study was also reviewed and approved by the Research Proposals Approval Committee (RPAC) of Eastern Health.

An informed consent document (Appendix C) was developed as per the suggested template from the HREA, and was approved along with the protocol. A study investigator reviewed this document with each potential subject. Time was given to review the document at home and bring forward any questions. After signing each subject was provided with a copy.

With respect to the choice of therapeutic agents, epoetin (Eprex®) and darbepoetin (Aranesp®) are competing products that are generally considered equally efficacious and have identical side effect profiles. Both drugs are given intravenously via dialysis machine ports with pre-filled syringes and are not associated with any discomfort or sensation during administration. The frequency of dosing did not affect the patients in

any way and the dialysis procedure was not prolonged or altered by administering one versus the other.

Complimentary drug was not provided by either manufacturer for this study and usual retail prices were paid for both. Both drugs have identical cost coverage with the Newfoundland and Labrador Prescription Drug Program (NLPDP) and all private insurance programs in this province. Currently, a nephrologist may prescribe either drug at their own discretion.

The only deviation from current clinical practice for subjects enrolled in this study was one additional CBC (complete blood count) per month during the run-in period. This represented an additional 10 mL of blood for testing per month, which was taken from the dialysis machine lines prior to dialysis and did not require venipuncture. This degree of blood loss was minimal and Hb was monitored closely throughout the study. Subjects were not subjected to any additional procedures, tests, surveys, interviews, or physical examinations.

## Chapter 4 Results

### 4.1 Subjects

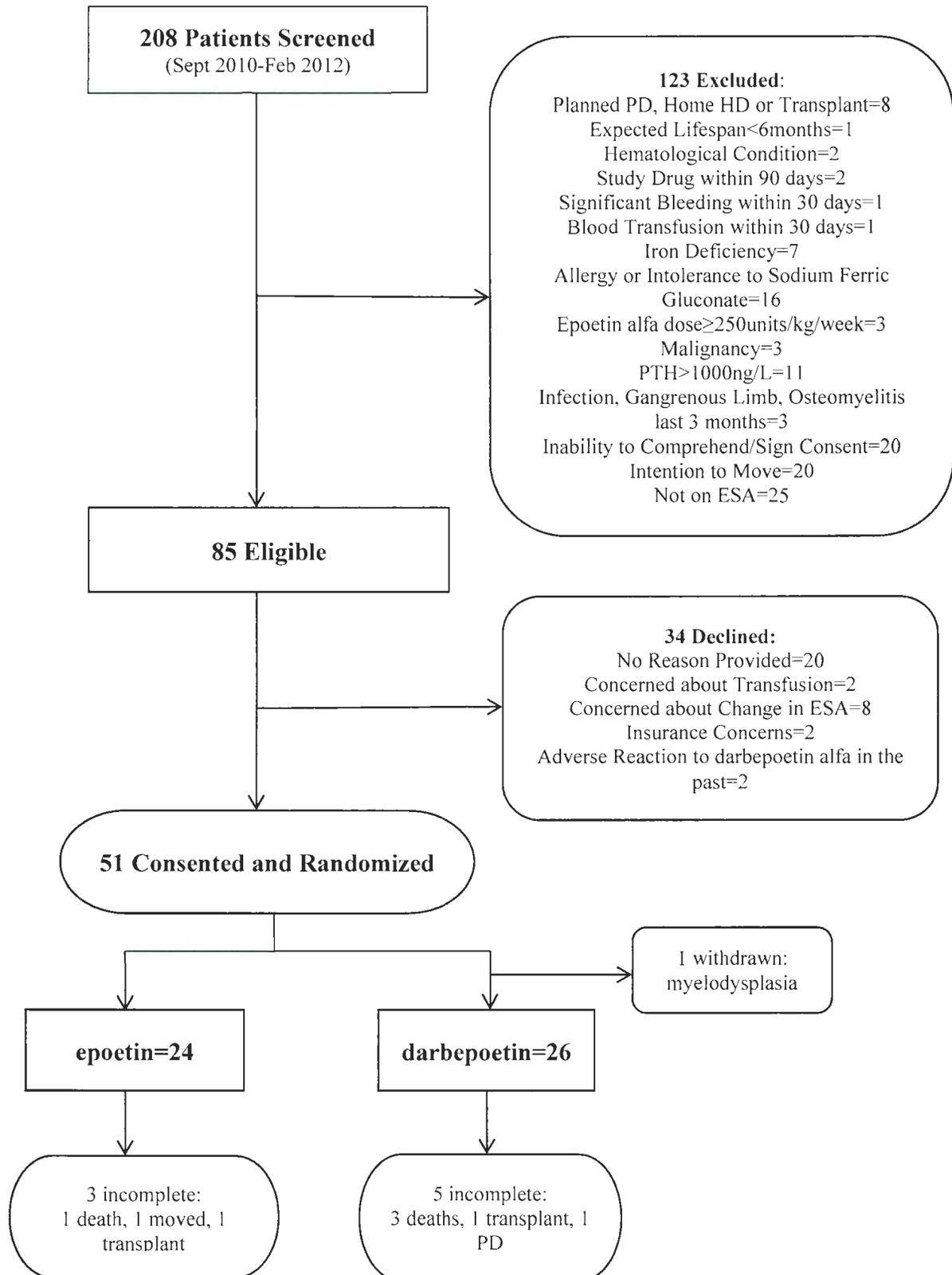
Figure 1 presents the flow of subjects through the trial. Between September 2010 and February 2012, 208 hemodialysis patients were screened for inclusion. Of these, 25 were not currently treated with an ESA and 98 met one of the exclusion criteria. The most common reasons for exclusion were an allergy or intolerance to Ferrlecit® (16), inability to comprehend and sign the consent document (20), or an intention to move to another centre (20). This left 85 eligible patients. The study investigator approached each eligible patient to explain the trial including the purpose and the implications for subjects. Each patient was provided with a copy of the consent document (Appendix C) to take away to read and consider at home. Within a week, the investigator met with the patient again to answer any questions and to complete the signing of the consent document if the individual had decided to participate. Of the 85 patients, 34 declined to participate and the reasons (if any) given were recorded and are outlined in Figure 1. Subsequently, 51 patients consented to participate and were randomized.

Of the 51 patients enrolled, 24 were randomized to the epoetin arm and 27 to the darbepoetin arm. Baseline characteristics are presented in Table 5. One subject in the darbepoetin arm was withdrawn from the study before the completion of the run-in phase due to the new diagnosis of a hematological condition. As dose stabilization did not occur, none of the data for this subject were included in the analysis. The final study groups consisted of 24 subjects in the epoetin arm and 26 subjects in the darbepoetin arm.

In the active phase, 8 subjects did not complete the full 12 months of follow up, 5 from the darbepoetin arm and 3 from the epoetin arm. Four of the patients died (after 2, 6, 7, and 9 months), one switched to peritoneal dialysis (after 6 months), one moved away unexpectedly (after 8 months), and 2 received kidney transplants (after 5 and 7 months). All of the data from these subjects were included in the final analysis with the last available month's data carried forward to the end.

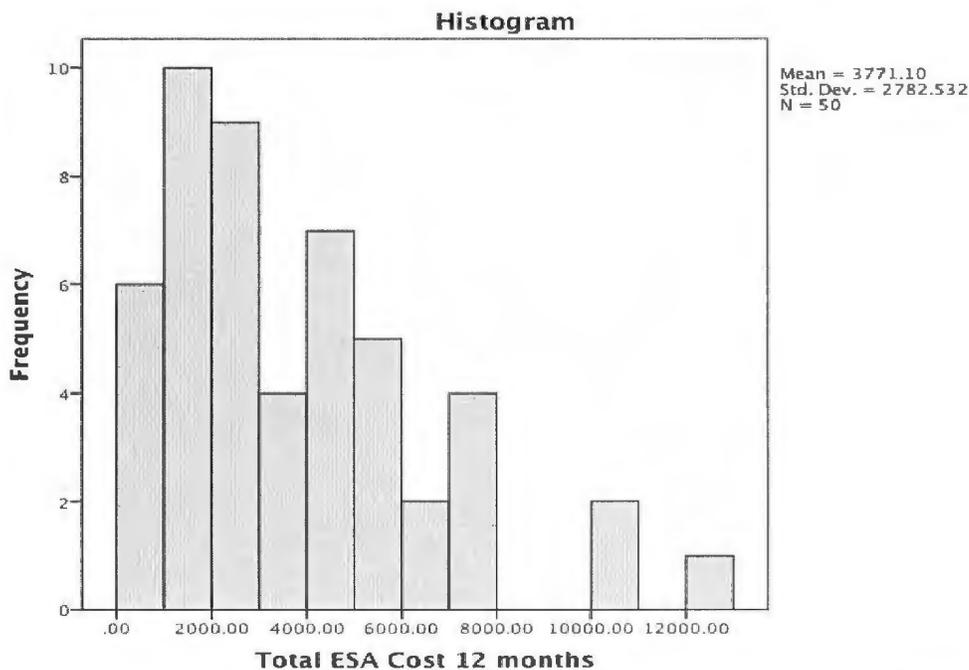
**Table 5: Demographics and Baseline Characteristics of Subjects**

	Epoetin(n=24)	Darbepoetin(n=26)
Age (mean±SD)	59.8 ± 13.3	61.0 ± 15.1
Male	13	20
Female	11	6
Baseline epoetin dose (units weekly, mean±SD)	6083 ± 3450	6654 ± 4749

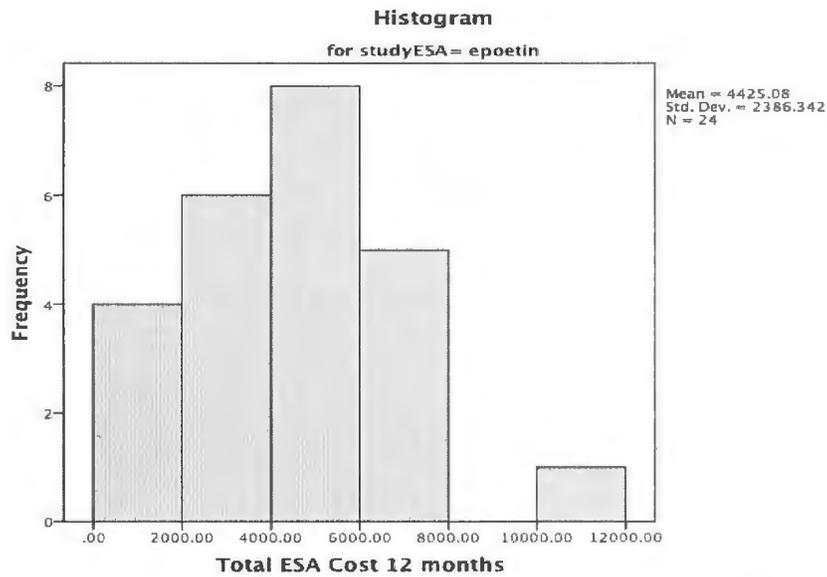
**Figure 1: Patient Flow Diagram**

#### 4.2 Primary Outcome – Total ESA Cost

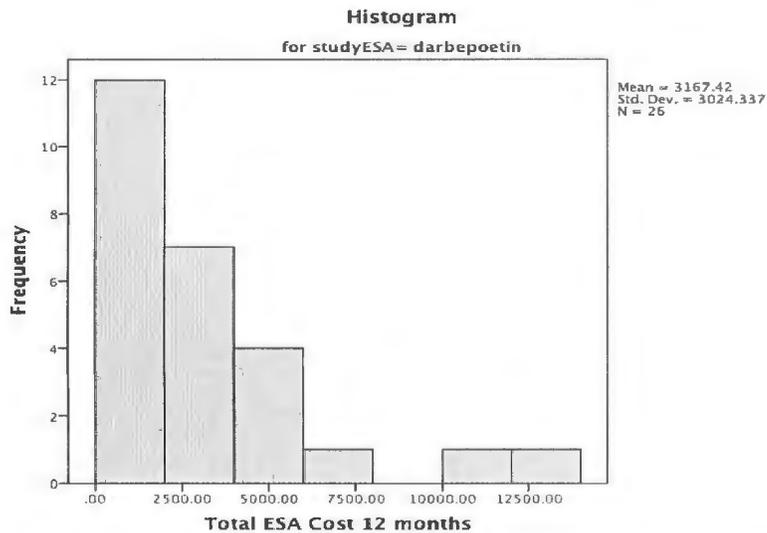
The histogram in Figure 2 demonstrates the distribution of the total ESA cost over the twelve month active phase. Skewness was 1.163 with a standard error of 0.337 and it does not meet the requirements for normality according to the Shapiro-Wilk test. When separated by study group, the distribution of total epoetin cost is normal (Figure 3), but darbepoetin continues to have a right skew (Figure 4). This necessitated the use of the nonparametric Mann-Whitney U test to compare groups as the independent t-test can only be used if the dependent variable is approximately normally distributed within each group.



**Figure 2: Distribution of Total ESA Cost over the 12 Month Active Study Phase (Epoetin and Darbepoetin Groups Combined)**

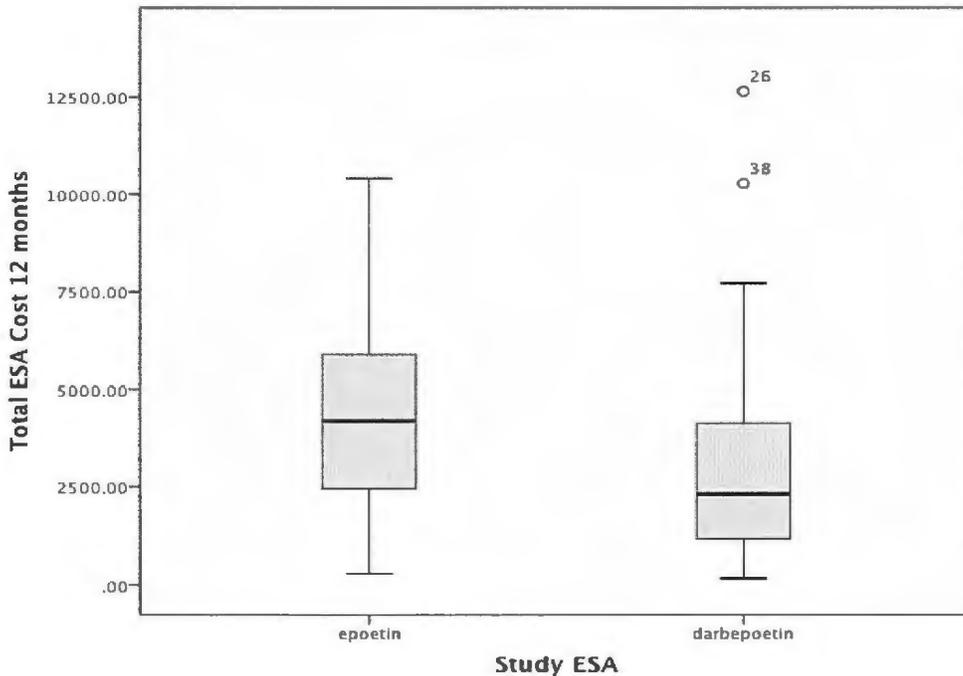


**Figure 3: Distribution of Total Epoetin Cost over the 12 Month Active Study Phase**



**Figure 4: Distribution of Total Darbepoetin Cost over the 12 Month Active Study Phase**

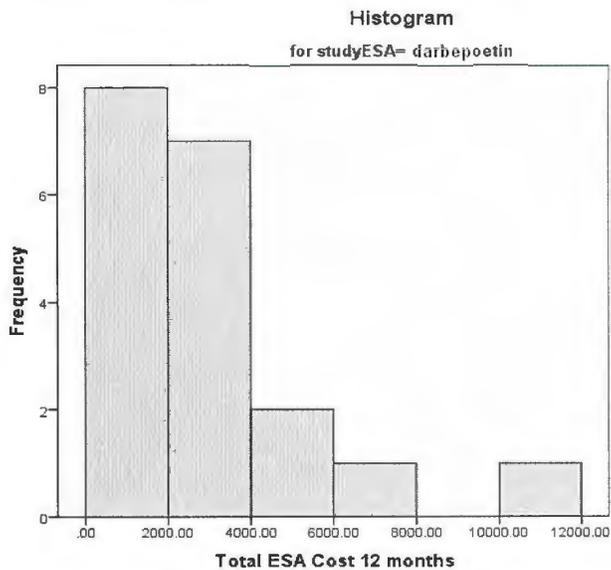
As is demonstrated in the boxplot in Figure 5, there was a major outlier (subject 26) in the darbepoetin arm. By the end of the active phase, the dose had escalated in this subject to the maximum dose of 150 $\mu$ g weekly and in the months after study completion the definition of ESA resistance was met in this case.



**Figure 5: Boxplot of Total Epoetin and Darbepoetin Cost over the 12 Month Active Study Phase Demonstrating Outliers**

To determine if this outlier was the cause for the skew in the darbepoetin data and if a case should be made to exclude this case, descriptive analysis was run with subject 26 excluded. As can be seen from Figure 6, the histogram for darbepoetin remains skewed with a value reported of 1.82 and a standard error of 0.524. The data still does not meet the requirements for normality according to the Shapiro-Wilk test. As a result, it was

determined that subject 26 was not the sole reason for the distribution of the data in the darbepoetin arm and all data were used in the analysis.



**Figure 6: Distribution of Total Darbepoetin Cost over the 12 Month Active Study Phase with Outlier Removed**

Results for the primary outcome and anemia targets are summarized in Table 6. The primary outcome was the total cost per patient of ESA required to maintain hemoglobin in the target range over 12 months. Total ESA cost was not normally distributed so results are expressed as median (interquartile range) and medians were compared using the Mann-Whitney U test.

The median total cost for epoetin over 12 months was \$4178.70(\$2416.37-5955.12) and for darbepoetin was \$2302.92(\$1177.86-4218.93). The median cost of darbepoetin was \$1875.78 less per year than epoetin and the difference was statistically significant ( $p=0.017$ ).

**Table 6: Comparison Between Epoetin and Darbepoetin Groups of Total ESA Cost and Anemia Targets During The 12 Month Active Study Phase**

Outcome	Epoetin (n=24)	Darbepoetin(n=26)	p Value
Total ESA Cost (\$) (median, IQR)	4178.70 (2416.37-5955.12)	2302.92 (1177.86-4218.93)	0.017 <sup>a</sup>
Hb (g/L) (median, IQR)	108.00 (106.00-112.71)	109.75 (105.88-116.08)	0.336 <sup>a</sup>
Ferritin (µg/L) (mean±SD)	847.58 ± 272.88	726.29 ± 377.13	0.202 <sup>b</sup>
TSAT (%) (median, IQR)	26.71 (22.46-32.33)	28.58 (23.90-33.75)	0.472 <sup>a</sup>
Iron Dose (mg.weekly) (median, IQR)	40.36 (20.83-59.90)	41.67 (19.53-70.96)	0.992 <sup>a</sup>
Total Iron Cost (\$) (median, IQR)	726.56 (375.00-1078.13)	750.00 (351.56-1277.34)	0.992 <sup>a</sup>

<sup>a</sup> Mann-Whitney U test <sup>b</sup> independent samples t-test

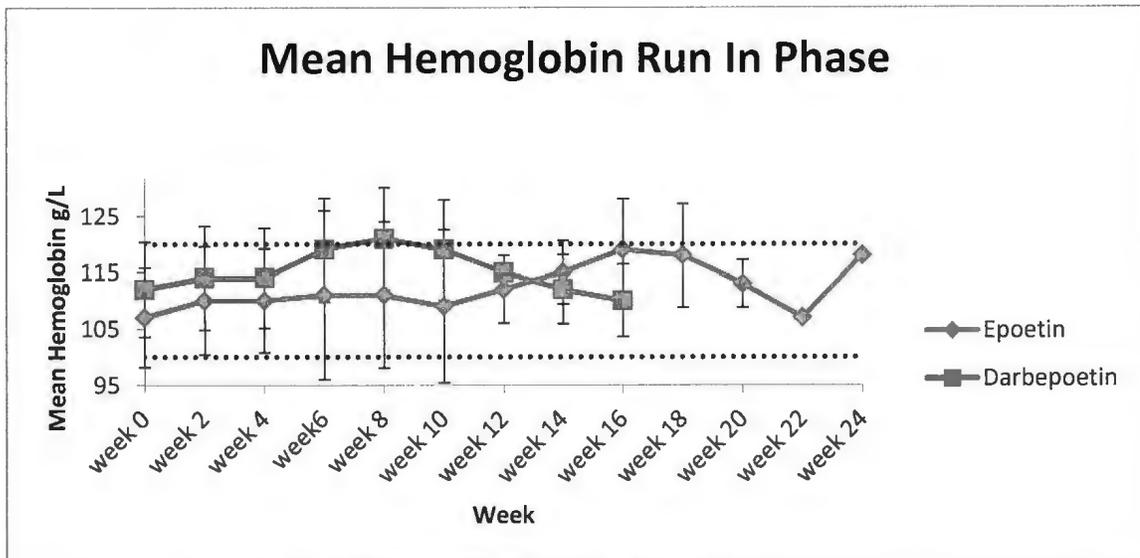
#### 4.3 Anemia Targets

As secondary outcomes, Hb, serum ferritin, TSAT, iron dose and iron cost were compared between the two groups. Of these, Hb, TSAT, iron dose and iron cost were not normally distributed so the Mann-Whitney U test was used to compare medians. Serum

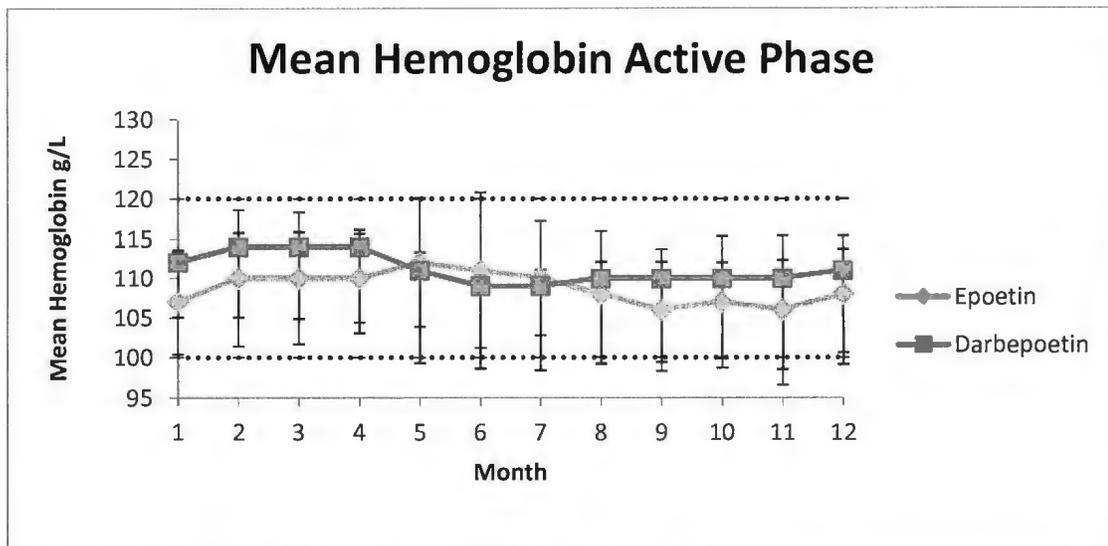
ferritin was normally distributed so the means were compared using the independent samples t-test.

There were no statistically significant differences between the two groups in any of the anemia targets compared. The median hemoglobin over 12 months was 108.0g/L in the epoetin group and 109.75g/L in the darbepoetin group ( $p=0.336$ ). Mean serum ferritin in the epoetin group was 847.58 $\mu$ g/L and the darbepoetin group was 726.29 $\mu$ g/L ( $p=0.202$ ). The median TSAT in the epoetin group was 26.71% and in the darbepoetin group was 28.58% ( $p=0.472$ ). The median weekly iron (Ferrlecit®) doses were not different with the epoetin group receiving 40.36mg and the darbepoetin group 41.67mg ( $p=0.992$ ). Median total annual iron (Ferrlecit®) cost was \$726.56 in the epoetin group and \$750.0 in the darbepoetin group ( $p=0.992$ ).

As stated above, the mean hemoglobin over the total 12 month study period was not different in the two arms. It is also of interest to know how the hemoglobin varied over the study period in both groups, particularly with respect to the target range of 100-120g/L. To examine this, the mean hemoglobin in each arm was determined for each two week period of the Run In Phase and for each month of the Active Phase. Figures 7 and 8 show the two phases graphed separately and Figure 9 is for the entire study period.

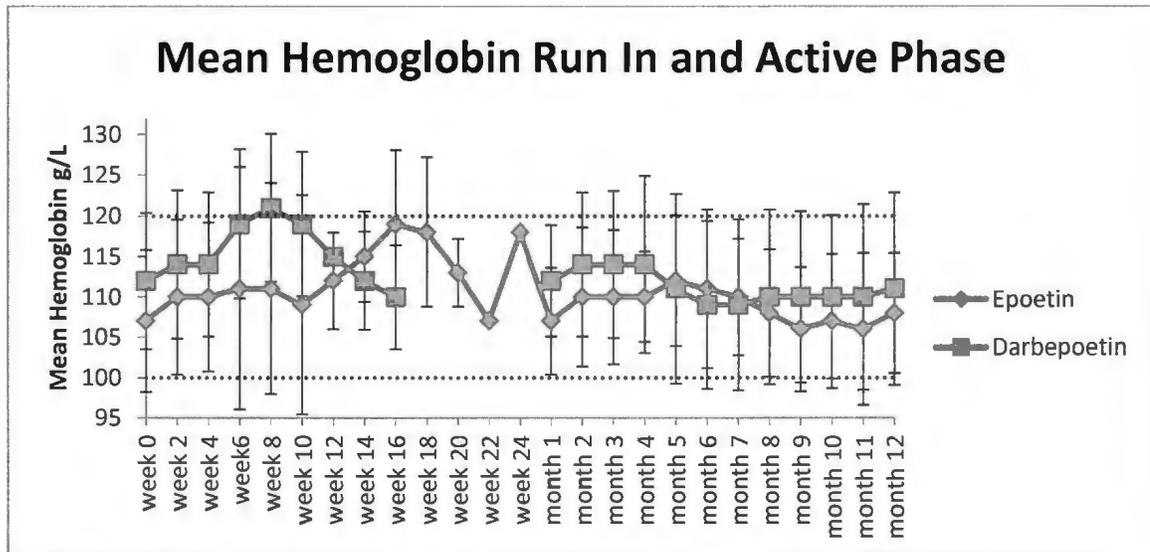


**Figure 7: Mean Hemoglobin ( $\pm$ SD) Run-In Phase**



**Figure 8: Mean Hemoglobin ( $\pm$ SD) Active Phase**

During the Run-In Phase (Figure 7), the mean Hb in both groups remained within the target range, with one exception in the darbepoetin arm during week 8 when the mean was 121g/L. As can be seen in Figure 8, both groups remained within the target during the Active Phase with minimal variation.



**Figure 9: Mean Hemoglobin ( $\pm$ SD) over Entire Study Period**

#### 4.4 Dose Stabilization

**Table 7: Comparison of Median Number of Dose Changes (IQR) and Median Number of Weeks to Dose Stabilization (IQR) between Epoetin and Darbepoetin Arms**

	Epoetin	Darbepoetin	p value*
Number Dose Changes Run-In Phase (median, IQR)	0 (0-1.75)	0 (0-0.25)	0.377
Number of Weeks to Stable Hb (median, IQR)	4 (4-12)	4 (4-8.5)	0.429
Number Dose Changes Active Phase (median, IQR)	2 (1-3)	2 (0-3.25)	0.843

\*Mann-Whitney U test

#### 4.4.1. Run-In

The number of dose changes and the weeks required to achieve hemoglobin stability (three consecutive Hb values in the target range, measured every 2 weeks) was determined and compared between groups. The data was not normally distributed. In the epoetin group, the median number of dose changes was 0 with an interquartile range of 0-1.75 and in the darbepoetin group the median number of dose changes was 0 with an interquartile range of 0-0.25 (Table 7). When compared using the Mann-Whitney U test, the difference was not significant ( $p=0.377$ ). The median number of weeks required to reach hemoglobin stability was 4 in both groups ( $p=0.429$ ) with an interquartile range of 4-12 in the epoetin group and an interquartile range of 4-8.5 in the darbepoetin group.

#### 4.4.2. Active Phase

The number of dose changes required to maintain hemoglobin in the target range during the active phase was determined and compared for each group. In the epoetin group, the median number of dose changes was 2 with an interquartile range of 1-3 and in the darbepoetin group the median number of dose changes was 2 with an interquartile range of 0-3.25. There was no significant difference in the medians ( $p=0.843$ ) when compared using the Mann-Whitney U test (Table 7).

#### 4.5 Dose Conversion Ratio

The dose conversion ratio was determined by dividing the average epoetin dose for each subject at the time of randomization by the average darbepoetin dose at three points in the

study - at the end of the run-in phase and at the 3 and 6 month intervals of the active phase. The mean dose conversion ratio at the end of run-in phase was 280:1 (95% CI 198-362:1). At the 3 month point of the active phase it was 360:1 (95% CI 262-457:1). At the 6 month point of the active phase it was 382:1 (95% CI 235-529:1).

A similar calculation was performed for subjects in the epoetin arm to determine the trend in dose required over the study time in this group. The epoetin dose for each subject at the time of randomization was divided by the epoetin dose at the end of the run-in phase and at the 3 and 6 month intervals of the active phase. The ratio at the end of the run in phase was 1.1:1 (95% CI 0.9-1.4:1), at the 3 month point of the active phase it was 1.2:1 (95% CI 0.6-1.9) at the 6 month point of the active phase it was 1.2:1 (95% CI 0.8-1.5) indicating that the epoetin doses were relatively stable.

## Chapter 5 Discussion

### 5.1 Study Design and Algorithm Based Management

There have been a number of observational switch studies, both prospective and retrospective, which have indicated that there may be a cost difference between darbepoetin and epoetin in the management of anemia in CKD. There is a lack of prospective, randomized controlled trials in this area. This research represents the first prospective, parallel group randomized controlled trial of intravenous epoetin and darbepoetin in hemodialysis patients with the primary outcome of cost.

Strengths of this study design include a run-in period to allow initial dose stabilization and a subsequent 12 month follow up which would be adequate to attain complete dose stabilization in the darbepoetin arm after the switch. In addition, the study was conducted only in hemodialysis patients and all ESAs were administered intravenously before and after randomization. An important component of the study was the use of a standard validated algorithm for ESA and iron dosing in all subjects with changes made only by the study investigator.

Numerous clinical guidelines have been published to direct the use of ESAs and iron.<sup>4, 7, 8</sup> Despite this, anemia often remains unrecognized and management is less than optimal. In a cross-sectional study of 8154 hemodialysis patients in the United States it was found that there was significant regional and patient-specific variation in anemia parameters.

Females, African Americans, patients 18-44 years of age and patients on dialysis for less than six months had significantly lower mean hemoglobin values despite having significantly higher epoetin doses than males, Caucasians, older patients and patients on dialysis for six months or more. There was also significant regional variation in the prescribing patterns for epoetin and iron.<sup>47</sup> Brimble et al published a randomized controlled trial of protocolized anemia management in hemodialysis patients in which 215 patients were randomized to anemia management with usual care or to management with an anemia management protocol. The primary outcome was the proportion of patient Hb values in the target range in the final 8 weeks of the 8 month study. The final proportions were not significantly different between the two groups (62% control, 63.6% protocol,  $p=0.8$ ). There was however a significant difference in epoetin dose in patients who remained in the study for longer than 5 months, the epoetin dose in the protocol group was 2788 units weekly less than the standard care group ( $p<0.05$ ), suggesting that a protocolized approach may provide similar results but with more efficient use of ESAs.<sup>48</sup>

As anemia management is primarily a medication-related activity, clinical pharmacists are ideally positioned to develop and administer anemia management protocols.<sup>47, 49</sup>

Pharmacist-implemented anemia management protocols have been found to provide significant clinical and economic benefits in a number of studies.<sup>50-55</sup>

In the Waterford Hospital Hemodialysis Unit of Eastern Health, a pharmacist managed anemia protocol has been in place since 2005. The protocol was developed by the clinical pharmacists in consultation with the Nephrologists of Eastern Health and it is updated

regularly to reflect current guidelines for ESA and iron use in hemodialysis patients. The current algorithms (Appendices A and B) have been used since 2009 and were developed using the most recent CSN guidelines<sup>4</sup>. Enrollment in this study began in the Fall of 2010 and the first patients were randomized in December 2010, so the algorithms were already being used in all patients at the Waterford for more than a year before the trial commenced. As part of the anemia management in this hemodialysis unit, monthly data is collected for anemia targets and ESA dose for all patients. From January to December 2010 the mean weekly epoetin alfa dose was 7715 units, the mean Hb was 109.6g/L and the mean proportion of Hb values in the target range (100-120g/L) was 74%. The mean proportion of TSAT values <20% was 16% and the mean proportion of serum ferritin values <200µg/L was 11%. The same algorithms were used in the study protocol. This likely contributed to the hemoglobin stability seen throughout the trial, particularly in the run-in phase.

## 5.2 Primary Outcome – Cost

The analysis of the primary outcome of total ESA cost over 12 months demonstrated a significant difference with darbepoetin costing \$1876 less per year per patient than epoetin. Considering the number of hemodialysis patients currently being treated with ESA for anemia and the high cost, a difference per patient of \$1876 would represent a significant cost savings to third party payers and to government.

The distribution of the total cost was not normal, so nonparametric analysis was used to compare medians. When the distributions were compared separately, it was found that epoetin costs were normally distributed but darbepoetin was not. In addition, there was a major outlier in the darbepoetin group in a patient who subsequently met the definition of ESA resistance. The analysis was run with this outlier removed to determine if it would change the distribution and it did not, the distribution of total cost for darbepoetin still had a large right skew.

### 5.3 Anemia Targets

It was important to determine if anemia targets were different between the two arms to validate any conclusions from the primary outcome data. If any of these were significantly different, it could account for a difference in required dose of ESA and subsequent cost. The main anemia indices used in clinical practice are Hb, serum ferritin and TSAT and in this study none of these displayed any statistically significant differences. In addition, if the dose of iron was different between the two arms it could account for a difference in ESA requirements so the mean weekly iron dose and total iron cost over 12 months were compared and these were not different. Both groups stayed within the target hemoglobin range over time with similar fluctuations when the mean hemoglobin was compared over the entire study period. Therefore, the difference in cost between epoetin and darbepoetin occurred when anemia management was comparable in both treatment groups.

#### 5.4 Dose Changes

Before entering the active phase of the trial, each subject had to demonstrate hemoglobin stability with three consecutive measurements within the target range. It was of interest to know if there was a difference in the time or number of dose changes required to achieve this stability, particularly when switching from epoetin to darbepoetin. The median number of changes required in the run-in phase was 0 in both groups with the interquartile range in epoetin group being 0-1.75 and in the darbepoetin 0-0.25, with no statistically significant difference. The number of weeks required to stabilize hemoglobin was also determined and again the difference between the two arms was not significantly different with a median of 4 weeks in each group.

The number of dose changes required in the active phase to maintain hemoglobin within the target range was also determined and compared, as this would be an indicator of hemoglobin variability. The median number of changes in the epoetin group was 2 with an interquartile range of 1-3 and the median number of changes in the darbepoetin group was 2 with an interquartile range of 0-3.25. The medians were not significantly different. While this was a secondary outcome and the trial was not designed to determine hemoglobin variability, this would indicate that there may not be a difference between the two ESAs. It is of interest to note that based on the dose conversion ratios the eventual dose of darbepoetin required in most cases was lower than at the start (which would have necessitated dose changes), yet there were still a comparable number of dose changes required in the epoetin arm where the overall dose remained relatively stable based on the ratios at the end of the run-in and at 3 and 6 months.

### 5.5 Dose Conversion Ratio

As was stated in the introduction, the dose conversion ratio of epoetin:darbepoetin has been extensively studied and while most have found it to be higher than the initial 200:1 ratio, there is much variability reported. It is generally agreed upon that predicting the dose conversion ratio is key to determining the relative cost of these agents. In an effort to estimate the dose conversion ratio in this study, it was calculated for subjects in the darbepoetin arm using the mean dose at the end of the run-in phase and at the 3 and 6 month points of the active phase. The rationale for the 6 month measure is that it has been suggested based on previous studies and the half life of red blood cells that it requires 5-6 months for patients to achieve a stable dose with darbepoetin.<sup>19,32</sup> At the end of the run-in phase the mean dose conversion ratio was 280:1, at the 3 month point it was 360:1 and at the 6 month point it was 382:1 indicating that the dose ratio is likely greater than 200:1 for most patients and this supports the finding of a cost advantage for darbepoetin over epoetin. This also supports the idea that the darbepoetin dose required does lessen over time when an initial 200:1 ratio is used to determine dose conversion from intravenous epoetin to intravenous darbepoetin, and dose stabilization is likely not achieved in the first few months.

### 5.6 Limitations and Challenges

It was challenging to enroll the desired number of subjects despite the number screened and the number found eligible. Of the 208 patients screened, 98 met one of the exclusion criteria. The most common reasons for exclusion were an inability to comprehend and

sign the consent document (20) or an intention to move to another centre (20). The number of patients unable to comprehend and sign consent is indicative of the demographics of the hemodialysis population, many of whom are elderly and in poor health with multiple comorbidities. A large number intending to move to another centre is the result of the distribution of hemodialysis units in this province. There are a several satellite dialysis units dispersed around the province, but most patients begin treatment in St. John's for medical reasons or while awaiting space in a satellite unit so at any given time there is a significant number of patients in the study centres that are planning to move soon. Intolerance to the intravenous iron product used in the study, Ferrlecit®, excluded another 16 patients. While iron intolerance is not uncommon, patients can often tolerate an alternate product (i.e. iron sucrose) however it was decided from the outset that it would be best to use only one iron product in the trial and this ultimately excluded sixteen potential subjects. In addition to these reasons, a number of patients (20) had characteristics which could lead to ESA resistance including high epoetin doses ( $\geq 250$  units/kg/week), malignancy, high PTH or ongoing infection. Thirty-four of the eligible patients declined to participate and the majority did not provide a specific reason but in general it was a concern of changing from their present therapy when they were currently feeling well. Again, many of these patients were elderly with multiple comorbidities. As these problems are common in all hemodialysis populations, recruitment for a trial like this will continue to be challenging.

As presented earlier, the sample size calculated to detect a difference of \$800 per patient per year for ESA with a 2-sided  $\alpha=0.05$  and power  $(1-\beta)=0.80$  was 112 subjects.

Participation was less than expected for reasons outlined above and when it became apparent that the desired number would not likely be recruited in a reasonable time period, enrollment was completed after 50 subjects were randomized. With a sample size of 50 subjects, using a 2-sided  $\alpha=0.05$  and a power  $(1-\beta)=0.80$ , a difference of \$1215 per year per patient in ESA cost could be detected.

Incomplete follow up occurred in a number of subjects. There were 8 cases and in each of these the last month's data was carried forward to the end and used in the analysis which could arguably create a bias. However if the increasing dose conversion ratio over time is considered, it would be expected that this carry forward method could potentially offer a bias favouring epoetin and not darbepoetin as one would expect the doses and cost of darbepoetin to decrease further in these patients if they had completed the 12 months.

A potential limitation in generalizing these results is that this study excluded patients who often require the highest doses including those with ESA resistance and iron intolerance. It also did not include many patients who were unable to comprehend and sign the consent form. Proponents of retrospective observational switch studies argue that their results are more applicable to the "real-world" scenario than a trial such as this as more patients are included. In patients with ESA resistance and iron intolerance there would possibly be less of a cost difference between the two ESAs as they tend to require higher doses of epoetin and would likely require higher doses of darbepoetin as well. On the other hand, there is some evidence in the literature to support a higher dose conversion ratio at higher doses of epoetin and if this is the case, one would expect a potential cost

advantage with darbepoetin in resistant cases. With respect to the elderly and those unable to consent, this population is generally not different from the general dialysis population in their ESA and iron requirements so it is arguable that these results could be applicable in these patients. As a pre-defined dosing algorithm was used in this trial, the results may not be generalizable to dialysis units without this approach to anemia management. This study was solely in hemodialysis patients receiving ESAs intravenously and therefore the results may not be the same in the non-dialysis CKD population or in groups where ESAs are administered subcutaneously.

The primary outcome measured in this trial is drug acquisition cost and non-acquisition costs were not considered. As previously discussed, Churchill et al conducted a study of non-acquisition costs associated with ESA administration<sup>44</sup> and found a cost savings with the less frequent administration required by darbepoetin. Time and motion techniques were used to determine nursing time for preparation and administration of the ESAs. A comparison of non-acquisition costs coupled with the drug cost outcome in our study would provide a more accurate picture of total cost savings between epoetin and darbepoetin. In addition to time in motion studies of nursing staff, it would be useful to study time in motion and inventory control requirements for pharmacy staff as darbepoetin requires a smaller number of syringes per prescription and in turn lower maintenance inventory levels. While this would be of interest, there is no data to suggest that non-acquisition costs would negate the results of this study.

## **Chapter 6 Summary**

This study was undertaken to determine if there is a cost difference between epoetin and darbepoetin when used intravenously in the management of anemia of chronic kidney disease in hemodialysis patients. To date there have been very few head-to-head comparisons of the two ESAs and the question has not been clearly answered. Most studies have been pre- and post-conversion comparisons in which results are difficult to interpret due to the absence of a control group and the tendency for ESA requirements to change in hemodialysis populations over time. Many of the studies were of subcutaneous administration, whereas the intravenous route is most commonly used in hemodialysis patients now. This is the first parallel group, randomized controlled trial with dose and cost as a primary outcome using the intravenous route in hemodialysis patients.

The results demonstrated that in this group of hemodialysis patients with comparable anemia management in both arms, darbepoetin cost \$1876 less per year per patient than epoetin. With approximately 90% of hemodialysis patients receiving ESAs in this province, it represents a costly component of care. A difference of this magnitude represents a significant cost savings and would help clinicians, policy makers and payers to make rational decisions about the choice of ESA used in this population.

The number of dose changes and the weeks required to achieve hemoglobin stability was compared between groups and found to be similar. There was no difference in the number

of dose changes required in the active phase. These results may indicate that there is no difference in the two ESAs with respect to hemoglobin variability.

The dose conversion ratios found in this trial support the concept of a cost advantage with darbepoetin. The ratios increased at both the 3 and 6 month intervals which seems to indicate that dose stabilization with darbepoetin does require several months.

A cost minimization analysis was conducted in an open label, parallel group, randomized controlled trial of fifty subjects. The results provide evidence for a cost advantage with intravenous darbepoetin alfa as compared to intravenous epoetin alfa in the management of anemia of chronic kidney disease in hemodialysis patients.

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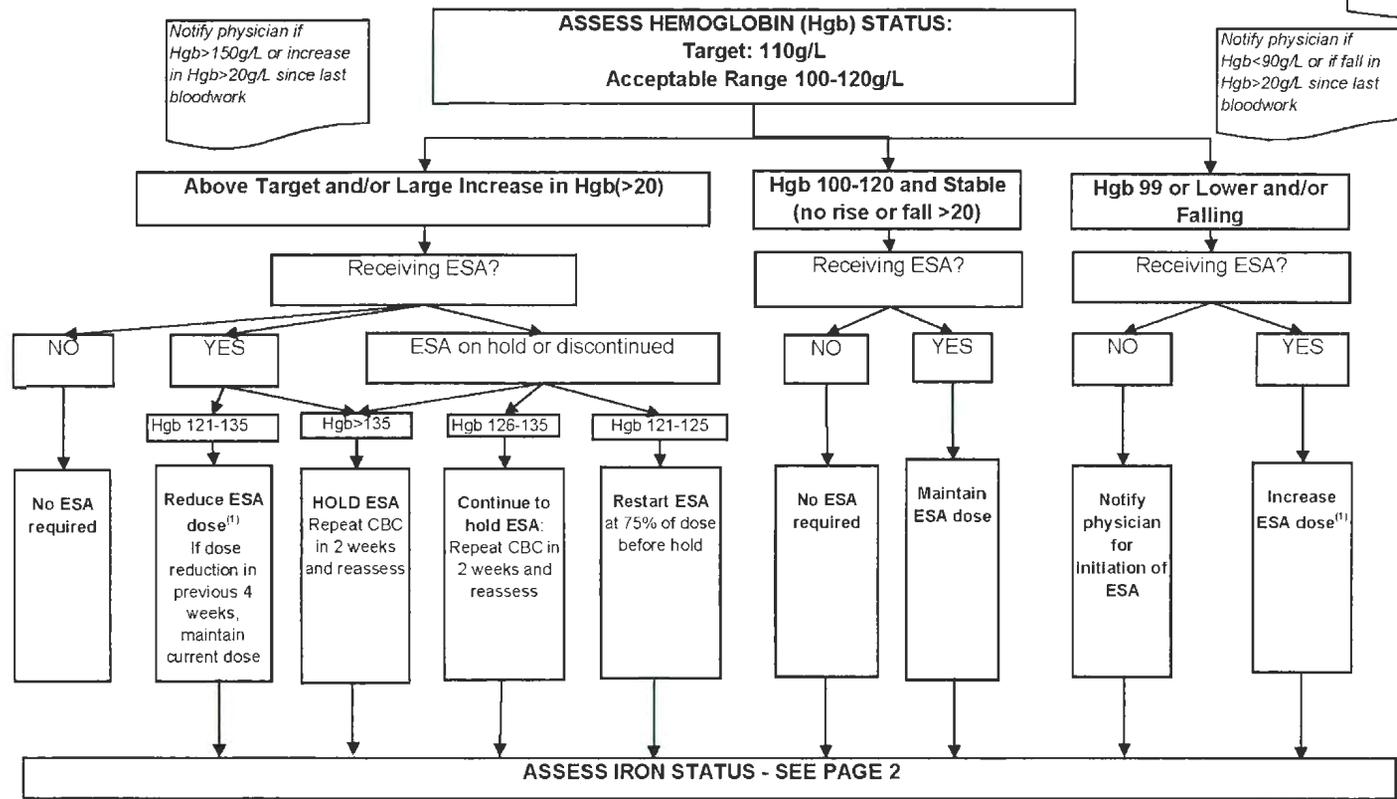
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Appendix A: Eprex®/Aranesp® (ESA) Dosing Algorithm

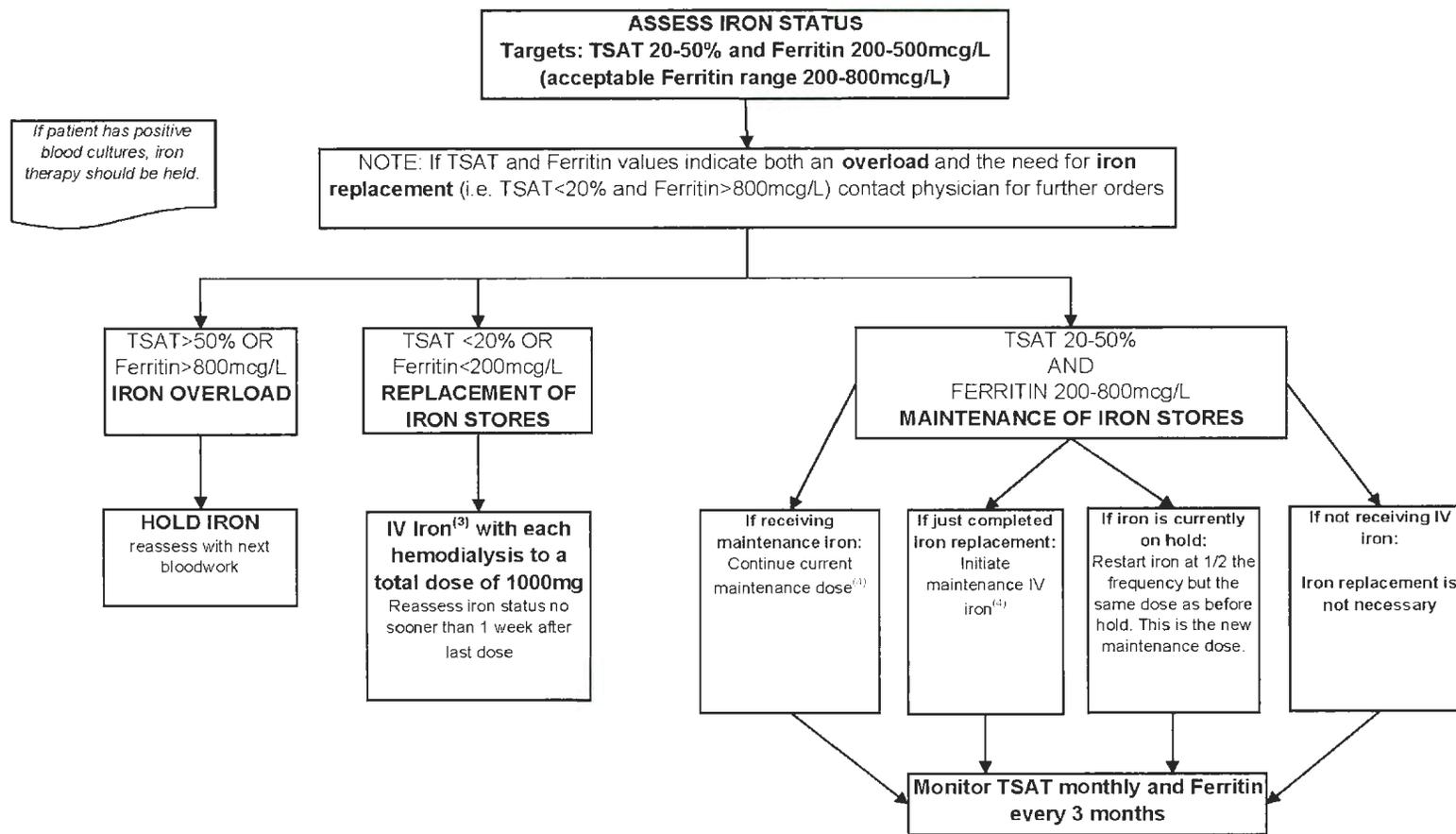
**Hemodialysis Anemia Management Algorithm**

ESA: Erythropoiesis Stimulating Agent (epoetin alpha or darbepoetin)



1) ESA Titration: 10-25% increments except when: -Hgb increase is < 5g/L/month, increase dose by 25-50%  
 -Hgb increase is > 20g/L/month, decrease dose by 25-50%  
 2) If epoetin alpha dose is >30 000ut/week or darbepoetin >150mcg/week for 2 months or more and Hgb <110g/L notify Nephrologist

**Appendix B: Ferrlecit® Dosing Algorithm**



3) Sodium ferric gluconate 125mg, Iron Sucrose or Iron Dextran 100mg . Give 25mg test dose if initiating Iron Dextran.  
4) Sodium ferric gluconate 62.5-125mg, Iron Sucrose or Iron Dextran 100mg **every 1-4 weeks**. Give 25mg test dose if initiating Iron Dextran.

**Appendix C****Memorial University and Eastern Health****Consent to Take Part in a Clinical Trial**

**TITLE:** A study comparing the cost of two drugs used to treat anemia in patients with chronic kidney disease on dialysis

**PROTOCOL TITLE:** A Randomized, Controlled Trial of Costs Associated with Anemia Therapy in Hemodialysis Patients Treated with intravenous Darbepoetin alfa versus Epoetin alfa

**Study Doctors:**

Dr. Sean Murphy  
Dr. Brendan Barrett  
Dr. Bryan Curtis

**Phone number:**

777-7226  
777-8073  
777-7226

**Researcher, Clinical Pharmacist:**

Andrea Woodland

777-3924 OR 777-3571

**Part A: General information****Introduction**

You have been invited to take part in a research study. Taking part in this study is voluntary. It is up to you to decide whether to be in the study or not. You can decide not to take part in the study. If you decide to take part, you are free to leave at any time. This will not affect your normal treatment.

Before you decide, you need to understand what the study is for, what risks you might take and what benefits you might receive. This consent form explains the study.

Please read this carefully. Take as much time as you like. If you like, take it home to think about for a while. Mark anything you do not understand or want explained better. After you have read it, please ask questions about anything that is not clear.

The researchers will:

- discuss the study with you
- answer your questions
- keep confidential any information which could identify you personally
- be available during the study to deal with problems and answer questions

We do not know if taking part in this study will help you. You may feel better. On the other hand, it might not help you at all. It might even make you feel worse. We can't always predict these things. We will always give you the best possible care no matter what happens.

You cannot take part in this research study if you are:

- Taking part in another drug study at this time
- If you have finished another drug study in the last 90 days
- If you have been in another research study in the last year you should tell the study doctor.

### Part B. Explaining this trial

#### 1. Why am I being asked to join this study?

You have been invited to take part in this study because your kidney disease has caused you to become anemic. This means that you have too few red blood cells in your blood. Red blood cells have hemoglobin which carries oxygen. You are already being treated with a drug – Erythropoietin – for this problem. Erythropoietin is a hormone made by the kidneys to help your body make red blood cells. When your kidneys cannot make enough of this hormone, you become anemic. This is common in patients with chronic kidney disease.

Two types of Erythropoietin are available in Canada to treat anemia. One is epoetin alfa (trade name Eprex®) and the other is darbepoetin alfa (trade name Aranesp®). You are currently taking Eprex ® for your anemia.

#### 2. What is being tested?

Eprex ® and Aranesp® are both approved for use in Canada and both seem to be equally effective for treating anemia. The cost of these drugs, however, may not be the same. It is difficult to compare them because they are dosed in different ways. This study will determine what the total costs are for each drug over a one year period.

**3. How many people will take part in this study?**

If you agree to take part, you will be one of 112 patients who will join this study in this province. This study is only being done in Newfoundland.

**4. What is the purpose of this study?**

The purpose of this study is to determine and compare the total costs for each drug over a one year period.

**5. How long will I be in the study?**

The study will be about 14 to 18 months long.

**6. How is the trial being done?**

If you are suitable and volunteer for this study, you will be randomized (picked by chance like the toss of a coin) to one of two groups:

1. Stay on Eprex<sup>®</sup>, the drug you are currently taking
2. Stop Eprex<sup>®</sup> and switch to Aranesp<sup>®</sup>

Aranesp<sup>®</sup> and Eprex<sup>®</sup> will be given on dialysis through the machine just as you are currently receiving your Eprex<sup>®</sup>. Eprex<sup>®</sup> may be given once, twice or three times a week, depending on the dose. Aranesp<sup>®</sup> will be given once a week or once every two weeks, depending on the dose. Your red blood cell level will be kept the same regardless of the group you are in.

Once you are randomized, you will know which group you have been put in.

**“Run-in” period (6 weeks +):**

Your red blood cell count must be in the correct range before we can collect data about the cost of your treatment. We will check your blood count (hemoglobin) every two weeks until it has been stable in the correct range for at least three measurements in a row. This will be done before your dialysis and blood will be taken through the machine. This means this part of the study will run for at least six weeks and possibly longer.

Based on your red blood cell levels, or if side effects occur, your doctor may change the dose or stop either drug. Depending on the amount of iron in your blood, you

may also receive intravenous iron for all or part of the study since both drugs need iron to work well. The adjustment of drug dose and the use of intravenous iron will be done in the same way as currently standard in the care of patients requiring dialysis.

**“Active study” period (12 months):**

Once your red blood cell count is in the correct range and stable for six weeks we will be able to collect data regarding the cost of your treatment. Your blood count still will be measured every four weeks for the remainder of the study. You will not have to do any special tests, questionnaires, or surveys. If any important medical events occur we may ask you about this.

**7. What will happen if I take part in this trial?**

If you are selected for the Eprex® group, the only change in your treatment will be one extra blood count measurement per month during the “run-in” period. The amount of extra blood will be approximately one teaspoonful, taken through the dialysis machine tubes. Our current practice is to check blood levels once monthly; this will stay the same during the active study period.

If you are selected for the Aranesp® group, your prescription will be changed to this drug. Because of the nature of this drug you will only receive it once a week or once every two weeks, but your hemoglobin level will be kept the same. The number and type of blood tests will be exactly the same as the other group.

**8. Are there risks to the study?**

**Switching from Eprex® to Aranesp®**

It is possible that your hemoglobin level will not be as well controlled on Aranesp® as it was on Eprex®, particularly in the early stages of this study. Your hemoglobin may become too low or too high, depending on your body’s response. This can usually be corrected with a change in dosage. Every effort will be made to keep your hemoglobin in the usual treatment range. Your hemoglobin will be checked every two weeks during the run-in phase to ensure your hemoglobin stays in the correct range and prevent it from going too far outside of it.

The chance of your hemoglobin becoming extremely high or low is very small. If your hemoglobin becomes extremely high, the drug may be stopped temporarily and some blood may be kept in the dialysis machine and thrown out after your

treatment. If your hemoglobin becomes extremely low your doctor may recommend a blood transfusion. It is very unlikely that these things will need to be done.

**Aranesp® and Eprex®**

Both of these medications are approved by Health Canada and are widely used in people with kidney disease. You are already taking Eprex®. Both drugs have similar possible side effects, including:

- High blood pressure or worsening of your high blood pressure. This may happen if your red blood cell level rises too quickly (reported in less than 2% of patients). In this case, your doctor will lower your dose of study drug.
- Rarely, very high blood pressures can result in headache, confusion, speech problems, or seizure (less than 1% of patients). This requires the immediate attention of your doctor in a hospital. If you have high blood pressure that is not well controlled, you will not qualify for this study.
- Severe allergic reactions are rare but may be life-threatening (less than 1% of patients).
- Rarely, (less than 1% of patients) patients have developed a reaction against erythropoietin (anti-erythropoietin antibodies) after treatment with approved erythropoiesis stimulating agents. In such patients, a condition called pure red cell aplasia (PRCA) can occur. This means that the red cells disappear slowly from the blood, as the bone marrow no longer makes them. The patient with PRCA becomes blood transfusion dependent, possibly for lifetime.
- For patients with chronic kidney disease, drugs that help your body make red blood cells may increase the risk of heart attack, stroke, blood clots and death when red blood cell levels go above 120 g/L. During this study drug doses will be kept at a level to keep your red blood cell level at or below 120 g/L. This is standard practice at our institution.

Please tell your doctor or the study staff right away if you think you are having side effects from your medication.

**Iron:**

Iron may be given to you through the study, as iron is required to produce red blood cells. Giving intravenous iron may be linked with the following side effects:

- common (1 or more in every 100 people): nausea, vomiting, diarrhea, headache, decreased blood pressure, dizziness, tiredness, back pain, joint pain, leg cramps, fever, swelling of lymph nodes
- rare (1 or more in every 10,000 people): allergic reaction, hives
- very rare (less than 1 in every 10,000 people): severe allergic reactions

**9. What About Pregnancy and Breast feeding?**

Women who are pregnant, or who intend to become pregnant or breastfeed will not qualify for this study. If you become pregnant during the study, you will have to stop participating in the study.

**10. Are there other choices?**

If you decide not to take part in this study, you will be treated as you currently are with no changes, with Eprex® once, twice, or three times a week to keep your hemoglobin stable.

**11. What happens at the end of the study?**

At the end of this study your doctor will discuss your treatment with you and advise the most appropriate drug for you.

**12. What are my responsibilities?**

If you take part in this study you will be expected to:

- come to all your dialysis sessions as you normally would
- follow the directions of the study doctor
- report all medications that you are taking or plan to take
- report any changes in your health
- report any problems you think might be related to taking part in the study

**13. Can I be taken out of the trial without my consent?**

Yes. You may be taken out of the study at any time if:

- the drug does not work for you
- you do not follow the directions of the study doctor
- if your study doctor feels side effects are harming your health

- there is new information which shows being in this study may not be in your best interest
- you become pregnant
- Health Canada or the ethics committee or your study doctor decides to stop the study

14. What about new information?

It is possible that we will get new information about a new treatment while you are in the study. You will be told about any new information that might affect your health or willingness to stay in the study. You will be asked whether you want to continue taking part in this trial.

15. Will it cost me anything?

Compensation

You will not be paid to be in the study. The study drugs will be provided and billed the same way your Eprex® is now. If you are switched to Aranesp® and paperwork is required for your insurance company, we will take care of this before the switch happens.

Research Related Injury

The medicine you will take in this study has already been approved for use in Canada. In the event that you suffer injury as a direct result of taking part in this study, normal legal rules on compensation will apply.

16. What about my privacy and confidentiality?

Protecting your privacy is an important part of this study. Every effort to protect your privacy will be made. However it cannot be guaranteed. For example we may be required by law to allow access to research records. A copy of this consent will be put in your health record. If you agree, your family doctor will be told that you are taking part in this study.

When you sign this consent form you give us permission to

- Collect information from you
- Collect information from your health record
- Share information with the people conducting the study
- Share information with the people responsible for protecting your safety

Access to records

The study doctor and members of the research team will see health and study records that identify you by name.

Other people may need to look at your health record and study records and

information that identify you. This might include

- the research ethics board for quality purposes
- Health Canada

They can look at your records only when one of the research team is present.

**Use of your study information.**

The research team will collect and use only the information they need to judge the safety and usefulness of the drugs.

This information will include your

- date of birth
- sex
- medical conditions
- medications
- the results of tests and procedures you had before and during the study
- information from study interviews and questionnaires

Your name and contact information will be kept secure by the research team in Newfoundland and Labrador. It will not be shared with others without your permission. Your name will not appear in any report or article published as a result of this study.

Information collected for this study will be kept as long as required by law. This could be 25 years or more.

If you decide to withdraw from the study, the information collected up to that time will continue to be used by the research team. It may not be removed.

After your part in this study ends, we may continue to review your health records. We may want to follow your progress and to check that the information we collected is correct.

Information collected and used by the research team will be stored by the Patient Research Centre, Eastern Health. The Manager of the Centre is the person responsible for keeping it secure.

**Your access to records**

You have the right to see the information that has been collected about you.

**17. What are my rights?**

**Signing this form gives us your consent to be in this study. It tells us that you understand the information about the research study. When you sign this form, you do not give up your legal rights. Researchers or agencies involved in this research study still have their legal and professional responsibilities.**

You can talk to someone who is not involved with the study at all. They can tell you about your rights as a participant in a research study. This person can be reached through:

*Office of the Human Investigation Committee (HIC) at 709-777-6974*

**Email: [hic@mun.ca](mailto:hic@mun.ca)**

**19. What about questions or problems?**

**If you have any questions about taking part in this study, you can ask your doctor. You can also meet with the doctor who is in charge of the study here at this institution. That person is:**

**Dr. Sean Murphy (709) 777-7226**

**OR**

**Andrea Woodland (709) 777-3924**

**After you have signed this consent form, you will be given a copy.**

**Signature Page**

**Study title:** A Randomized, Controlled Trial of Costs Associated with Anemia Therapy In Hemodialysis Patients Treated with intravenous Darbepoetin alfa versus Epoetin alfa

**Name of principal investigator:** Dr. Sean Murphy and Andrea Woodland

**To be filled out and signed by the participant:**

Please check as appropriate:

I have read the consent [and information sheet].	Yes { } No { }
I have had the opportunity to ask questions/to discuss this study.	Yes { } No { }
I have received satisfactory answers to all of my questions.	Yes { } No { }
<b>I have received enough information about the study.</b>	<b>Yes { } No { }</b>
I have spoken to Dr. _____ and he/she has answered my questions.	Yes { } No { }
I understand that I am free to withdraw from the study	Yes { } No { }
1. at any time	
2. without having to give a reason	
3. without affecting my future care	
I understand that it is my choice to be in the study and that I may not benefit.	Yes { } No { }
I agree that the study doctor, the study sponsor or a regulatory agency may read the parts of my hospital records relevant to the study.	Yes { } No { }
I understand how my privacy is protected and my records kept confidential.	Yes { } No { }
I agree to take part in this study.	Yes { } No { }

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Signature of participant	Name printed	Year Month Day
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Signature of person conducting the consent discussion	Name printed	Year Month Day
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<i>Signature of witness [if applicable]</i>	<i>Name printed</i>	<i>Year</i>
<i>Month Day</i>		

**To be signed by the investigator:**

I have explained this study to the best of my ability. I invited questions and gave answers. I believe that the participant fully understands what is involved in being in the study, any potential risks of the study and that he or she has freely chosen to be in the study.

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Signature of investigator	Name Printed	Year Month Day
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Telephone number: \_\_\_\_\_

