Incorporation of Uncertainty into a Medical Decision Model of Erythropoietin Use in Premature Infants at Risk for Red Cell Transfusion

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CERTIFICATE OF APPROVAL

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Has been approved

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ABSTRACT

Premature infants are at risk of developing significant anemia with adverse clinical outcome, yet blood transfusions used to treat anemia carry additional risks. Studies have investigated the use of recombinant erythropoietin (r-Epo) to reduce the need for blood transfusions. The beneficial impact of r-Epo use is controversial, and the original studies and meta-analyses were hampered by significant heterogeneity across trials, particularly in gestational age/birth weight, r-Epo dose, and transfusion criteria, as well as variation in the quality of evidence.

Medical decision analytic models offer an advantage given the ability to combine evidence from multiple sources, and to focus the analysis on the outcomes of specific interest to the decision maker. However, standard approaches to address uncertainty in medical decision modeling seldom account for the uncertainty related to the quality of the evidence. A medical decision model was created to evaluate the cost-effectiveness of either long or short course r-Epo treatment in premature infants less than 1500 g birth weight to prevent blood transfusions. The model combined data from previous r-Epo trials as well as more recent evidence on adverse outcomes related to either r-Epo or blood transfusion. In addition, uncertainty related to the quality of the evidence was incorporated into the model. Probabilistic sensitivity analyses revealed that the choice of no r-Epo treatment was cost-effective in the majority of sample runs, with lower cost and increased effectiveness as compared to long or short r-Epo treatment, and remained the optimal choice over a wide range of willingness-to-pay thresholds.

INTRODUCTION

Premature infants are at risk of developing significant anemia, due to diminished production of red blood cells in the bone marrow immediately after birth. This drop in red blood production is related to postnatal suppression of erythropoietin, an endogenous hormone that stimulates red cell production. This anemia of prematurity is exacerbated by the volume of blood required for routine laboratory testing in critically ill patients (especially given the small size and circulating blood volume of premature infants), as well as the reduced lifespan of neonatal red blood cells as compared to those of adult patients.(1)

The risks of anemia, given the significant drop in circulating hemoglobin (Hgb), include decreased oxygen delivery to tissues, reduced cardiac output, poor growth and possibly apnea.(2) In general, the risk increases with progressively lower Hgb levels, however the clinical impact on the infant also depends on the infant's severity of illness. Given these risks, premature infants often receive red cell transfusions to treat significant anemia. However, transfusion of blood products also carries risk, including transfusion reactions and transmission of blood borne infections. More recently, concern has been raised regarding possible lung injury, intestinal injury, and increased mortality in critically ill children who have received blood transfusions.(3-6) There is also a significant cost with transfusions, and the supply of blood products available for transfusion is limited.

There have been many investigations of the use of recombinant erythropoietin (r-Epo) in premature infants to reduce the need for red blood cell transfusions. A meta-analysis (7) of studies of "late" r-Epo treatment, i.e. beyond the 7th day of life, in premature infants revealed that administration of r-Epo modestly reduced the use of any transfusions, the total number of transfusions per infant, and the total volume of blood transfused per infant. r-Epo use did not reduce the number of donor exposures, however, particularly since many of the smallest, most critically ill premature infants had already received red cell transfusions prior to study entry. There was significant heterogeneity across the studies analyzed, including variation in the gestational age/birth weight of the study infants and the Hgb threshold used for transfusions (liberal vs. restrictive), both of which impact the probability of transfusion, as well as differences in r-Epo dose (long or short course), and the amount of iron supplementation. There was also variation in the quality of studies related to design, sample size, concealment of allocation, and blinding of treatment received. There were no differences in other short-term, clinical outcomes, but assessment of these short-term adverse outcomes was inconsistent, and long-term neurodevelopmental outcomes were not reported.(7)

In an attempt to prevent anemia and initial blood transfusions in sick, premature infants, studies of the use of "early" r-Epo treatment, that is in the first 7 days of life, have been reported. A meta-analysis of these studies also demonstrated reductions in the overall number and volume of transfusions, but early r-Epo treatment did not prevent early blood transfusions during the first few weeks of life (given the lag time to treatment effect), and comparison of early vs. late r-Epo treatment regimens demonstrated no significant difference in overall transfusion requirements.(1) In addition, there was an

increased risk of severe retinopathy of prematurity (ROP) associated with early r-Epo treatment as opposed to late r-Epo treatment.(1,8) The etiology of the increased risk of ROP with early r-Epo use is unclear. r-Epo is an angiogenic compound, and may promote excessive vascular growth and retinopathy with higher cumulative doses, as seen in some the early r-Epo trials with longer treatment courses. It may also be associated with the use of IV iron supplements (early r-Epo trial patients were not on feedings and often given IV iron) or higher iron supplement doses, as iron is a known oxidant.(8,9) Given the concern regarding severe ROP with early r-Epo treatment, use of r-Epo in premature infants to prevent transfusions is usually modeled after the late r-Epo trials.

Results of cost-effectiveness studies of the use of r-Epo in premature infants have been mixed, as benefit from r-Epo treatment varied with study design, liberal vs. restrictive transfusion criteria, and patient characteristics. In addition, most of these studies focused on costs alone.(1,10-12)

Use of r-Epo in premature infants to reduce the risk of transfusion remains controversial. Since completion of the r-Epo studies in the late 1990s, most neonatal intensive care units have adopted more restrictive transfusion criteria, which reduces the frequency of transfusions, as well as directed donor banking and division of adult blood units into smaller satellite packs in order to reduce donor exposure.(2,13) Despite this, many infants continue to receive transfusions.(14,15) Therefore, many neonatologists continue to use late r-Epo treatment for premature infants at risk of transfusion (40% of respondents in one survey (2)), and cite the outcomes of the published, randomized, controlled trials as evidence of benefit, often without consideration of the heterogeneity of the trials and the quality of the studies.

The objectives of this study were: 1) to review methods that incorporate uncertainty of the evidence into a cost-effective analysis, and 2) to perform a cost-effectiveness analysis of the use of late r-Epo treatment in premature infants to prevent blood transfusions that uses these methods to incorporate uncertainty into the decision model.

Trial Designs and Meta-Analyses

The randomized controlled trial (RCT) is held as the gold standard of trial designs, given the weaknesses and biases of non-randomized, uncontrolled trials that may affect the outcome of the study. However RCTs may suffer from sample size limitations, and other issues of internal validity related to the study design and analysis, which cause inconsistencies in outcome effects between trials. In addition, RCTs may suffer from poor external validity; it may be difficult to generalize the findings of the RCT to routine practice if there are differences in patient characteristics, disease severity, as well as variation in treatment implementation or variation in the treatment alternatives available, as compared to that reported in the trial.(16) For example, an RCT may have enrolled patients with a lower severity of illness than that seen in clinical practice, and the lower severity of illness may have lessened the benefit of the treatment that would have otherwise occurred had patients with a more severe level of illness been enrolled. Similarly, older patients are often excluded from RCTs given the presence of other chronic illnesses that may confound the analysis; attempts to generalize the results of the trial to a population that would have been excluded is also problematic.(17)

Organizations creating clinical guidelines may rely on trial design as a surrogate for evidence quality, without characterizing the quality of the evidence provided by the trial or a quantification of net benefit or cost-effectiveness.(18) Grading systems have been established that rate the quality of evidence and the strength of the recommendations, but poor agreement between the various grading systems and low reproducibility of judgments have been reported.(19)

Meta-analysis of multiple trial results may address uncertainties related to small sample sizes of individual trials. However, the quality of a meta-analysis is dependent on the quality of the individual studies utilized.(20) The use of summary scores to identify trials of high quality for meta-analysis is problematic; Jüni et al reported a lack of significant association of quality summary scores with the treatment effect.(21) Meta-analysis is also affected by heterogeneity in patient characteristics, disease severity, enrollment criteria, intervention, and outcome assessments across studies. Interactions between the studied intervention and patient characteristics may modify the effect of the intervention, and if substantial, the average effect observed across trials may not apply to subgroups of patients.(17) Subgroup analysis may be helpful in determining differences in treatment effect across groups, but multiple subgroup comparisons raise the probability of false-positive conclusions, or may result in a loss of power to detect differences, given the small n of trials in each subgroup.(20,22) Meta-regression has been used to address heterogeneity across studies, however the relationship between the average patient characteristics and estimates of the treatment effect across trials may not be the same as this relationship within trials.(22) Ultimately, heterogeneity across studies, or the

inclusion of only those trials with narrow, matching criteria may reduce the external validity of a meta-analysis and limit applicability in routine, clinical practice.

Medical Decision Models

Medical decision analytic models assess the probability-weighted consequences of various decision alternatives and provide a net impact of various options.(16) Medical decision models offer an advantage because they may combine data from multiple sources, and use both direct, and indirect sources of data for analysis. The models may then focus on quantifying outcomes of specific interest to the decision maker. This is particularly useful in pediatrics, as applicable, direct data are often limited.(18) Medical decision models may also quantify uncertainty, as opposed to relying on study design as the indicator of uncertainty.(18) Medical decision modeling may provide information regarding cost-effectiveness not present in the RCTs, and may provide value of information analysis to determine if collection of additional parameter information through further research is advantageous and not cost-prohibitive.(16) Medical decision models, however, contain a degree of uncertainty related to variability across subgroups and populations, and to variability from random chance. They also may contain a degree of uncertainty from model structure, from model parameters, and from limitations of the underlying evidence.(23-25)

Uncertainty in Medical Decision Models

Heterogeneity of patient characteristics, such as age, gender, and risk factors, may lead to variation in treatment effects and costs, and introduce uncertainty into the decision model. This uncertainty related to patient heterogeneity may be addressed using repeated

analysis of a model using subgroup-specific parameter values to derive subgroup-specific outcomes. The distribution of expected outcomes across subgroups reflects the impact of population/subgroup differences on the modeled outcome.(26)

Stochastic, or first order, uncertainty represents uncertainty of patient-level outcomes due to random chance. For example, first order Monte Carlo (patient-level) microsimulation generates subjects one at a time, and their path through the model is determined by a random number generator and the probabilities at each node. Tracker variables (counters) capture payoffs of the random walks through the model. Thus chance occurrence within the microsimulation determines values downstream in the model and reflects stochastic uncertainty.(24)

Model uncertainty reflects uncertainty from the model structure, including the choice of alternatives, outcome consequences and types of payoffs, as well as choices in analytic methods such as discounting of benefits. This may be quantified by repeating the analysis using alternative assumptions to evaluate the impact of these assumptions on the model results. If there is no major impact, one may justify use of a single, best model. If there is significant impact, one may present results of each analysis, or provide a weighted combination of the results.(23,24)

Parameter uncertainty represents uncertainty of parameter value estimates, such as probabilities or payoff values, across multiple data sources. Standard statistical methods are deterministic: they consider parameters to have a true value, and use point estimates in analysis. Simple 1- or 2-way sensitivity analysis using extreme values from confidence ranges may reveal the impact of parameter value variation on the outcome.

However, using point estimates for parameter values ignores the uncertainty of parameter values drawn from across multiple data sources, and simple 1- or 2-way sensitivity analysis does not address the simultaneous variation of multiple model parameters.(27,28) A probabilistic approach to parameter uncertainty considers the parameter to be a random variable that can take a range of values.(27) Probabilistic sensitivity analysis (PSA) using Monte Carlo simulation addresses parameter uncertainty by randomly assigning values to each parameter derived from a probability distribution specified for each parameter, creating a sample of parameter values for each run through the model. Distributions are assigned based on the type of parameter and prior estimates of these parameters across studies. Multiple sample runs are performed, using a distinct sample of randomly derived values for each run. Thus, PSA propagates uncertainty represented in each parameter distribution forward through the model, and more adequately addresses the issue of simultaneous variation of multiple model parameters.(29,30) However, possible issues with PSA include distributions chosen to represent parameter uncertainty, and assumptions of parameter independence. In addition, PSA may not reflect the quality of evidence from which the parameter values are derived.(25,31)

Uncertainty of the Quality of Evidence used in Medical Decision Models

A key advantage of decision analytic modeling is the ability to combine data from multiple sources to focus on the decision maker's outcome of interest, rather than an outcome determined strictly within the RCT. Analyses commonly address random error of parameter values derived from individual sources, but often do not account for the uncertainty related to the quality of the evidence. PSA using parameter probability

distributions determined only by the type of parameter and the prior distribution ignores uncertainty in the strength of the evidence, and the applicability of the data to the model's target population.(25) Approaches to define a more precise parameter probability distribution have been reported, including multiple-bias modeling,(32) and Bayesian approaches such as the confidence profile method,(33) both of which explicitly model biases and incorporate these biases in the parameter distribution. For example, the confidence profile method derives a posterior parameter distribution using the prior distribution, a likelihood function based on the type of experiment, type of outcome and effect measure, as well as a function that adjusts for the bias.(33) While these techniques yield a more precise distribution estimate, they require the analyst to determine each bias, quantify the impact of that bias and modify each distribution for that bias, adding significant complexity to the modeling. It may also be impossible to identify and quantify each bias.(25)

Braithwaite, et al (25) have reported a simplified approach to incorporating the quality of evidence into decision modeling. They modified the US Preventative Services Task Force method for grading evidence to create a simplified hierarchy that ranks study design, internal validity, and external validity, and used this hierarchy to judge the evidence. If the quality of the evidence was judged sufficient, the parameter distribution was based on the statistical uncertainty of the qualifying data source, and when more than one source met the qualifying grade of evidence, the data source with the most statistically precise estimate was used. However, if the data source has poor-quality evidence, it was not used. Rather, it was assumed that little is known about the parameter's true value and instead used uninformative probability distributions, such as

uniform distributions where it is equally likely that the parameter has any value in the specified range. This technique was applied to a model of directly observed therapy for individuals with newly diagnosed HIV infection. Fewer than one fifth of the data sources received a "qualifying" grade of evidence, and quality adjusted outcomes and the cost-effectiveness estimates derived using only high-quality evidence differed substantially from those results obtained using all sources of evidence. This simplified approach offers a more transparent and feasible method for incorporating uncertainty of evidence into medical decision models.(25)

Summary and Selected Approach for Evaluation

The use of r-Epo treatment in premature infants remains controversial. The original r-Epo trials had significant differences in study design and varied in quality, and the meta-analysis of these studies was affected by this heterogeneity. Most cost-effectiveness studies of late r-Epo use in premature infants relied on cost differences alone and did not account for quality of the evidence or heterogeneity among trials.

A medical decision model was created to evaluate the use of r-Epo treatment in premature infants at risk for transfusions. Specifically, cost-effectiveness of either long or short course r-Epo vs. no r-Epo treatment was compared against no use of r-Epo. Uncertainty of the quality of evidence was incorporated into the model using techniques described by Braithwaite et al.(25) The model was analyzed using probabilistic sensitivity analysis to account for parameter uncertainty.

METHODS

Decision Model

The target population of the model was premature infants less than 1500 g birth weight. The primary decision was whether or not to use late r-Epo treatment, and the model was run first representing a long (18 dose) course of r-Epo, then representing a short (10 dose) course of r-Epo. The model's primary risk of r-Epo therapy in premature infants was severe ROP requiring laser treatment, which usually results in visual impairment. Risk for severe ROP has been identified across several studies of early r-Epo use,(8) but there was no significant change in risk of retinopathy for the infants found within the late r-Epo trials.(7) However, only 3 late r-Epo trials (34-36) reported on all grades of retinopathy, and only 2 trials reported on severe retinopathy.(34,37) While the FDA has placed a black box warning on r-Epo use regarding risk of adverse events including hypertension, myocardial infarction, stroke and mortality, these were seen only with r-Epo use in adults, primarily in cancer patients and patients with existing cardiovascular disease. None of these risks, however, have been identified across the multiple studies of early or late r-Epo use in premature infants, and therefore were not modeled within the decision tree.

The model included risks of blood transfusion: transfusion-acquired infections - HIV and Hepatitis (B or C), acute fatal and acute non-fatal hemolytic transfusion reactions, and intestinal injury, specifically necrotizing enterocolitis (NEC). The model assumed clinical resolution of medical and surgical NEC outcomes by discharge. There

has been evidence for increased risk of acute lung injury and mortality with blood transfusions in critically ill adults and older children.(6) Premature infants may share these risks, however the effect of transfusions on mortality and acute lung injury have not been well studied in this population. In addition, there was no significant effect of late r-Epo use (and it's modest reduction in transfusions) on mortality or bronchopulmonary dysplasia, a chronic lung disease of premature infants, but the treatment effect or sample sizes may have been too small to see a change.(7) Similarly, randomized controlled studies of restricted vs. liberal transfusion policies in premature infants did not find a difference in mortality or lung injury.(13,14) Therefore, acute lung injury and mortality from blood transfusion (aside from NEC-associated mortality) were not included in the decision model.

Hospitalization costs included baseline costs for premature infant survivors and non-survivors without NEC, as well as costs of medical and surgical NEC survivors and non-survivors. Treatment costs included the cost of either long or short course r-Epo, and the cost of each blood transfusion. The remaining itemized complication costs (NEC is factored into the hospitalization costs) included the additional costs over baseline of: laser treatment and follow up for severe ROP, fatal and non-fatal transfusion reactions, the treatment of HIV infection, and the treatment of chronic Hepatitis. Effectiveness was modeled using utilities representing the various outcome states factored over the first year of life. The decision tree is shown in Figure 1.

Literature Search

To determine the evidence-based risk of blood transfusion in premature infants with and without r-Epo treatment, studies from the original 2006 (updated 2010) meta-analysis of late r-Epo treatment by Aher and Ohlsson were obtained.(7) The study by Juul et al (38) was eliminated given the use of oral r-Epo (as opposed to the typical subcutaneous or IV delivery), and the study by Donato et al (39) was irretrievable, even in abstract form. In addition, a literature search was performed using the strategy [infant, newborn OR infant, premature] AND [erythropoietin/*] AND [blood transfusion/*] yielding 3 additional r-Epo trials.(9,40,41) Haiden et al (40) was eliminated as early r-Epo treatment was used. The studies by Shah et al, and Birenbaum et al (9,41) were included, however the timing of the r-Epo treatment (i.e. early vs. late) was not specified, and neither study was a randomized, controlled trial.

Cases of NEC have been temporally associated with red blood cell transfusions. A literature search was performed using the strategy [infant, newborn OR infant, premature] AND [enterocolitis, necrotizing/*] AND [erythrocyte transfusion/adverse effect*], yielding 5 studies. (4,5,42-44) Various search terms were used in combination to identify studies reporting on the remaining risks, costs and effectiveness utilities of r-Epo treatment and blood transfusions, including [infant, newborn OR infant, premature], [erythropoietin/*], [blood transfusion/*], [enterocolitis, necrotizing/*], [retinopathy of prematurity/*], [erythrocyte transfusion/adverse effect*], [HIV/*], [Hepatitis B, chronic], [Hepatitis C, chronic], [cost benefit analysis/], [cost utility OR cost-utility], [cost effectiveness OR cost-effectiveness], [quality-adjusted life years]. In addition, data on

standard premature infant outcomes from the Vermont Oxford Network, a national neonatal network database, were reviewed.(45)

Quality Evaluation and Parameter Estimation

Studies were evaluated for the quality of evidence using a modified U.S. Preventive Services Task Force valuation hierarchy as described by Braithwaite et al.(25) Three domains were evaluated: study design, internal validity, and external validity. Study design ranked the research design from true randomized, controlled trial (best, level 1) through expert opinion (worst, level 3). Note that observational studies may have also qualified as level 1 if used to estimate an observational parameter data that cannot be obtained experimentally, particularly if observational parameter data were derived from large sample reports from multiple centers.(25) Internal validity was ranked as good if the study met all criteria for that particular design, fair if it did not meet all criteria but had no fatal flaw, or poor if the study design contained a fatal flaw. External validity was ranked as high if the study met all of the criteria (e.g. similarity of sample, intervention, and clinical / environmental circumstances to that in clinical practice), and low if it did not meet all criteria.

In addition to standard criteria, three criteria specific to r-Epo trials were used to evaluate internal and external validity: r-Epo dose, iron supplement dose, and the use of a strict transfusion policy. Studies have demonstrated a superior r-Epo treatment effect (reduction of transfusion risk) using "high" doses, that is $\geq$ 500 units/kg/week, rather than "low" r-Epo doses below that threshold, and high dose r-Epo treatment is used currently in clinical care. Doses greater than 750 units/kg/week yield no additional benefit in

reducing transfusions, although no additional risk was identified.(1,46) Therefore, use of high r-Epo dose was required to meet internal and external validity criteria. The iron supplementation dose is also critical, and high iron supplementation doses ($\geq$ 4 mg elemental iron/kg/day, as used in clinical practice) are required to generate an adequate hematologic response. (1,34,47) Therefore, use of a high iron supplement dose in both control and treatment groups was required to meet internal and external validity criteria. Finally, reports have demonstrated that the transfusion risk may be reduced with the use of strict transfusion guidelines alone, as opposed to either lack of any guidelines, or liberal transfusion policies to maintain higher hematocrits. Use of liberal transfusions to maintain an artificially high hematocrit in premature infants exaggerates the r-Epo treatment effect, as repetitive transfusions suppress endogenous erythropoietin production.(1,34,48,49) Therefore, a strict transfusion policy was required for a study to meet internal and external validity criteria.

Twenty-eight trials of late r-Epo use in premature infants (9,34-37,41,47,50-70) were identified, and were evaluated for risk of transfusion and risk of ROP, with and without r-Epo treatment, using the valuation hierarchy. The evaluation results are listed in Table 1, with comments justifying the ranking listed in Table 2. Four of the 28 studies were ranked as high quality studies.(34,35,37,47) Similarly, 5 studies of NEC in premature infants following blood transfusion were identified, (4,5,42-44) with 2 studies being higher quality, case-control studies (5,42) as compared to the remaining retrospective cohort studies, as listed in Table 3. The studies for the remaining parameters were similarly ranked, and parameter estimates were derived from the highest quality sources. If multiple studies were identified of equal quality and precision of statistical

analysis, pooled estimates were calculated for proportions and for means and standard deviations.(71)

Distributions were assigned to each parameter based on the quality of the data source and the level of uncertainty of the parameter estimate. Estimates derived from high quality randomized, controlled trials with good internal and external validity, as well as those derived from high quality observational data drawn from national samples were assigned a normal distribution for continuous data, and a beta distribution for proportions, utilizing mean and standard deviations.(72-74) Estimates derived from lower quality data sources were assigned a uniform distribution as a way to incorporate this uncertainty into the model, (25) utilizing a range of 0.5 to 1.5 times the pooled estimate, except for widely disparate estimates in which case the low and high values were used to specify the range.

Risk Parameters

The decision model targeted late r-Epo use after the first week of life for infants less than 1500 g birth weight. The probability of transfusion and the mean number of transfusions per infant for long course r-Epo (18 doses) were derived as pooled estimates from studies by Al-Kharfy et al (37) and Shannon et al.(34) The remaining two high quality studies of long course r-Epo were not included; the study by Meyer et al (47) enrolled less ill premature infants with a later gestational age and greater weight at birth, and the study by Maier et al (35) restricted enrollment to those infants less than 1000 g birth weight. The probability of transfusion and the mean number of transfusions per infant for short course r-Epo (10 doses) were derived from Reiter et al.(62) The

remaining study of short course r-Epo by Whitehall et al,(68) did not include probability of transfusion estimates and was less statistically precise.

The transfusion-associated risks were modeled as a single event given the current practice of multiple transfusions being drawn from one donor. The risk of transfusion-acquired Hepatitis was derived as a pooled estimate of risk of Hepatitis B and Hepatitis C infections.(75) Baseline probabilities of NEC and ROP were obtained from the 2009 key performance measures for standard level III neonatal intensive care units (45) as reported by the Vermont Oxford Network, a national neonatal database reporting on premature infants less than 1500 g birth weight. NEC was modeled as either medical or surgical NEC. The widely disparate estimates of transfusion-associated NEC from two higher quality studies (5,42) were used as the upper and lower range limits of the odds ratio of NEC following any transfusions, and this in turn was used together with the baseline probability of NEC to calculate the actual probability of NEC following and transfusion. Note: although some of the trials of late r-Epo use reported the incidence of NEC in the placebo and treatment groups, none reported the proportion of NEC in relation to transfusion. The risk of severe ROP after r-Epo use was derived from the 95% confidence interval limits of the incidence of severe ROP in the high-quality late r-Epo trials, as reported in the meta-analysis by Aher and Ohlsson.(7) Table 4 lists estimates and corresponding distributions for all risk parameters.

Cost Parameters

The cost-effectiveness evaluation was designed from a societal perspective. Cost estimates are expressed in 2011 dollars using medical inflation calculations based on

information from the Bureau of Labor Statistics.(76) The costs of r-Epo treatment and blood transfusions were derived from Fain et al.(10) The cost of r-Epo treatment included the costs of medication, pharmacy preparation and nurse administration, and was adjusted for a long (18 dose) vs. short r-Epo course (10 dose). The cost of each blood transfusion included the costs of laboratory screening, blood product, blood bank preparation, irradiation, CMV screening, IV tubing, and nurse administration. The cost of laser treatment and follow up of severe ROP was derived from Jackson et al (77), and included the cost of extended consultation and follow up exams by the retinal specialist and laser treatment. The cost was adjusted to include one outpatient follow up exam by the retinal specialist during the first year of life. The annual cost of chronic Hepatitis reflected that of Hepatitis B (78) given its higher prevalence and risk from blood transfusion. The annual cost of HIV was assigned the costs from the HAART era as described by Wilson et al.(79) Hospitalization costs for premature infant survivors and non-survivors, including those without NEC (pooled estimates), those with medical NEC, and those with surgical NEC, were derived from Bisquera et al,(80) using a cost to charge ratio of 0.41 to convert from the Texas hospital charges used in the study.(81) Table 5 lists estimates and corresponding distributions for all cost parameters.

Utilities

The model represents outcomes to one year of life. The utility of severe ROP requiring laser surgery used residual visual impairment calculated from the Snellen visual acuity decimal, and the distribution was assigned a range representing unilateral to bilateral impairment.(77,82) The point estimate for HIV infection was derived from Mrus et al,(83) and the distribution range limits used were utility estimates for phases II

and IV of HIV infection, as described by Holtgrave, et al.(84) Outcome possibilities for NEC included death and resolution of the process by discharge. Utilities specific for NEC survivors were not available. The utility of resolved surgical NEC was estimated using that reported for infants with short gut syndrome post surgical repair.(85) The utility of resolved medical NEC was estimated to be higher than that for surgical NEC and chronic hepatitis, and the distribution ranged from 0.87 - "survival with some home medical support",(86) to 1.0 - perfect health. Survival without any complication was given a utility of 1.0, as was survival complicated only by non-fatal transfusion reaction, as there are usually no serious, long-term sequelae.(78,87) Death was given a utility of 0. Final effectiveness was reported as quality adjusted life year, the product of the one year time frame and the utility for each outcome state. Utilities were multiplied together to represent outcome states with multiple complications. Table 5 lists estimates and corresponding distributions for all utility parameters.

Analysis

Analysis was performed using TreeAge Pro Suite 2009 (TreeAge Software, Williamstown, MA). Probabilistic sensitivity analysis was run for both long course, and short course r-Epo treatment using 1000 samples and a willingness-to-pay threshold of $50,000 per unit of effectiveness. Acceptability curves of the probability of cost-effectiveness for r-Epo dosing regimens were created over a willingness-to-pay range of $0 to $100,000.

RESULTS

Long course r-Epo treatment

Mean estimates of cost-effectiveness from the 1000 sample probabilistic sensitivity analyses for long and short r-Epo treatments are shown in Table 6. The mean incremental cost of a long course of r-Epo was $647, and was associated with a decreased incremental effectiveness of 0.008. The choice of no r-Epo treatment dominated long course r-Epo treatment because it had lower cost and higher effectiveness, and was considered cost-effective in this population.

Figure 2 demonstrates a scatter plot of each pair of incremental cost and incremental effectiveness values for all 1000 runs for a long course of r-Epo vs. no r-Epo treatment. The dashed line represents the willingness-to-pay threshold of $50,000. Sixty one percent of the sample runs were located in the upper left quadrant, indicating higher cost and lower effectiveness for r-Epo treatment. In addition, only 15% of sample runs demonstrated cost-effectiveness for r-Epo treatment at a willingness-to-pay threshold of $50,000 (i.e. pairs located in the three remaining quadrants that were to the right and below the willingness-to-pay threshold line). The probability that r-Epo was cost effective across a willingness-to-pay range of $0 to $100,000 was always less than 0.2 (Figure 3). Note that the probability of cost-effectiveness for no r-Epo treatment did not exceed 90%, which reflected uncertainty in the model. The no r-Epo treatment option dominated that of long course r-Epo even at high willingness-to-pay thresholds.

Short course r-Epo treatment

The mean incremental cost of a short course of r-Epo was $330, and was associated with a decreased incremental effectiveness of 0.008. The choice of no r-Epo treatment dominated short course r-Epo treatment because it had lower cost and higher effectiveness, and was considered cost-effective in this population.

Figure 4 demonstrates a scatter plot of each pair of incremental cost and incremental effectiveness values for all 1000 runs for a short course of r-Epo vs. no r-Epo treatment with a willingness-to-pay threshold of $50,000. Seventy three percent of the sample runs were located in the upper left quadrant, indicating higher cost and lower effectiveness for short course r-Epo treatment, similar to that seen with a long r-Epo course. In addition, only 10% of sample runs demonstrated cost-effectiveness for short r-Epo treatment at a willingness-to-pay threshold of $50,000. The probability that r-Epo was cost effective across a willingness-to-pay range of $0 to $100,000 was always less than 0.15 (Figure 5). The no r-Epo treatment option dominated that of short course r-Epo even at high willingness-to-pay thresholds. Therefore the model found the no r-Epo treatment option to be the optimal cost-effective choice as compared to either long course or short course r-Epo treatment.

DISCUSSION

The goal of evidence-based, medical practice is to use the best scientific evidence to guide medical decision making. Randomized controlled trials may avoid biases found in non-randomized, uncontrolled trials, however trial design alone is not a good surrogate for evidence quality. Meta-analyses may address uncertainties related to sample size, however meta-analyses are influenced by the underlying quality of the individual trials, as well as heterogeneity across trials, e.g. among the subject populations, treatment strategies, and outcome assessments. In addition, the meta-analysis results are limited to the context of the study designs, and therefore may not be generalizable to current clinical practice if practice strategies have changed.

The meta-analysis of late r-Epo trials by Aher and Ohlsson (7) combined trials of different dosing regimens (short vs. long course, high vs. low dose r-Epo, high vs. low dose iron supplements), different transfusion strategies (liberal or strict), different populations (trials restricted to smaller sicker infants together with trials of larger, less ill infants at lower risk of transfusion), and trials with varying degrees of quality. The meta-analysis showed a significant effect on the use of one or more (i.e. any) transfusions, the number of transfusions and the transfused blood volume using late r-Epo therapy, however acknowledged the significant heterogeneity across the trials as well as the issue of possible transfusions given to infants in the first week of life prior to initiation of late r-Epo therapy.(7) The meta-analysis attempted to analyze individual subgroups of trials based on r-Epo dose, transfusion strategies and study quality. However, each subgroup

reflected only one issue of the trials (dose or transfusion strategy or quality), and heterogeneity persisted. The I^2 calculation, a measurement of the percentage of total variation across studies due to heterogeneity rather than pure chance, (88) was 74% for the "use of one or more transfusions" outcome when all studies were included, and was 58% when studies were restricted to high quality trials as judged by the authors.(7) In addition, the meta-analysis did not contain an assessment of cost-effectiveness.

Medical decision modeling allows inclusion of both direct and indirect data from multiple sources, and may be tailored to focus on quantifying outcomes of specific interest to the decision maker. Models may incorporate uncertainty and may be used for cost-effectiveness analysis. There has been increased push for cost-effectiveness analyses of medical care, with the use of probabilistic sensitivity analysis to assess parameter uncertainty.(24) However, probabilistic sensitivity analysis by itself does not address the uncertainty in the quality of data sources.

The results of prior cost-effectiveness studies of r-Epo treatment in premature infants have been mixed, and have focused primarily on the costs of treatment and costs of adverse events.(1,10-12) This project focused on the cost-effectiveness of late r-Epo treatment, included outcome states to one year of life, and incorporated uncertainty regarding the quality of the evidence into the decision model. The decision analysis suggests that the no r-Epo treatment option is the optimal, cost-effective choice as compared to either long or short course r-Epo treatment, and remains so across a wide range of willingness-to-pay thresholds.

There are limitations to this project's decision analysis. Use of other distribution types to represent uncertainty, or calculation of specific posterior distributions may have provided a more precise analysis. Specific utilities for some outcome states were not readily available, however non-informative, uniform distributions were used to represent these parameters within the model. Similarly, the evidence for risk of ROP with r-Epo use, and for risk of NEC following blood transfusion were both uncertain, however these were also represented as uniform distributions with ranges that reflect the current evidence.

The model assumed clinical resolution of medical and surgical NEC outcomes by discharge. A small percentage of surgical NEC cases will persist with short gut syndrome and have additional cost and morbidity post-discharge, however post-discharge cost estimates were not readily available. Future work may include determination of short gut syndrome costs and outcomes through one year of life and incorporation into the model.

The decision model does not specifically quantify donor exposure. Most of the late r-Epo trials did not report donor exposure. Extremely premature infants often receive blood transfusions during the first week of life, and therefore may have already had a donor exposure prior to the window for possible late r-Epo treatment. Also, the more current practice of dividing an adult blood unit into smaller satellite packs for use with small premature infants may reduce donor exposure, and further complicated the estimation of donor exposure using data derived from the original r-Epo trials. Future work may include incorporation of donor exposure, based on further analysis of more current data, into the decision model.

Clinical Implications

Given the modest effect of r-Epo on transfusion risk, the use of r-Epo in premature infants to attempt to reduce blood transfusions is not cost-effective. Efforts to reduce transfusions through reduction in blood sampling for laboratory tests and stricter transfusion criteria, as well as use of satellite packs to reduce donor exposure may be more cost-effective strategies for neonatal care.

CONCLUSION

Using a medical decision model configured to incorporate uncertainty of the evidence regarding the use of late r-Epo treatment in premature infants to prevent blood transfusions, a cost-effectiveness analysis has shown that both long course and short course r-Epo treatments are not cost-effective as compared to the no r-Epo treatment option.

REFERENCES

1. von Kohorn I, Ehrenkranz RA. Anemia in the preterm infant: erythropoietin versus erythrocyte transfusion - it's not that simple. Clin Perinatol 2009; 36:111-123

2. Kirpalani H. iNICQ Presentation: Controversies, Anemia of Prematurity. Vermont Oxford Network Conference. November 10, 2010

3. Luban NL. Transfusion safety: where are we today? Ann NY Acad Sci 2005; 1054:325-341

4. Mally P, Golombek SG, Mishra R, Nigam S, Mohandas K, Depalhma H, et al. Association of necrotizing enterocolitis with elective packed red cell transfusions in stable, growing premature neonates. Am J Perinatol 2006; 23:451-458

5. Christensen RD, Lambert DK, Henry E, Wiedmeier SE, Snow GL, Baer Vl, et al. Is "transfusion-associated necrotizing enterocolitis" an authentic entity? Transfusion 2010; 50:1106-1112

6. Kneyber MC, Hersi MI, Twisk JW, Markhorst DG, Plötz FB. RBC transfusion in critically ill children is independently associated with increased mortality. Intensive Care Med 2007; 33:1414-1422

7. Aher SM, Ohlsson A. Late erythropoietin for preventing red blood cell transfusion in preterm and/or low birth weight infants. Cochrane Database of Systematic Reviews 2006, Issue 3. Art. No.:CD004868, updated 2010

8. Ohlsson A, Aher SM. Early erythropoietin for preventing red blood cell transfusion in preterm and/or low birth weight infants. Cochrane Database of Systematic Reviews 2006, Issue 3. Art. No.:CD004863, updated 2010

9. Shah N, Jadav P, Jean-Baptiste D, Weedon J, Cohen LM, Kim MR. The effect of recombinant human erythropoietin on the development of retinopathy of prematurity. Am J Perinatol 2010; 27:67-72.

10. Fain J, Hilsenrath P, Widness JA, Strauss RG, Mutnick AH. A cost analysis comparing erythropoietin and red cell transfusions in the treatment of anemia of prematurity. Transfusion 1995; 35:936-943.

11. Shireman TI, Hilsenrath PE, Strauss RG, Widness JA, Mutnick AH. Recombinant human erythropoietin vs. transfusions in the treatment of anemia of prematurity. A cost-benefit analysis. Arch Pediatr Adolesc Med 1994; 148:582-588.

12. Meyer MP, Haworth C, McNeill L. Is the use of recombinant human erythropoietin in anemia of prematurity cost-effective? S Am Med J 1996; 86:249-251.

13. Maier RF, Sonntag J, Walka MM, Liu G, Metze BC, Obladen M. Changing practices of red cell transfusions in infants with birth weights less than 1000 g. J Pediatr 2000; 136:220-224

14. Kirpalani H, Whyte RK, Andersen C, Asztalos EV, Heddle N, Blajchman MA, et al. The premature infants in need of transfusion (PINT) study: a randomized,

controlled trial of a restrictive (low) versus liberal (high) transfusion threshold for extremely low birth weight infants. J Pediatr 2006; 148:730-734

15. Bell EF, Strauss RG, Widness JA, Mahoney LT, Mock DM, Seward VJ, et al. Randomized trial of liberal versus restrictive guidelines for red blood cell transfusion in preterm infants. Pediatrics 2005; 115:1685-1691

16. Claxton K, Cohen JT, Neumann PJ. When is evidence sufficient? Health Affairs 2005; 24:93-101

17. Greenfield S, Kravitz R, Duan N, Kaplan SH. Heterogeneity of treatment effects: implications for guidelines, payment, and quality assessment. Am J Med 2007; 120:S3-S9

18. Cohen JT, Neumann PJ. Using decision analysis to better evaluate pediatric clinical guidelines. Health Affairs 2008; 27:1467-1475

19. Atkins D, Eccles M, Flottorp S, Guyatt GH, Henry D, Hill S, et al. Systems for grading the quality of evidence and the strength of recommendations I: critical appraisal of existing approaches. The GRADE working group. BMC Health Services Research 2004; 4:38-44

20. Yuan Y, Hunt R Systematic reviews: the good, the bad and the ugly. Am J Gastroenterol 2009; 104:1086-1092

21. Jüni P, Witschi A, Bloch R, Egger M. The hazards of scoring the quality of clinical trials for meta-analysis. JAMA 1999; 282:1054-1060

22. Reade MC, Delaney A, Bailey MJ, Angus DC. Bench-to-bedside review: avoiding pitfalls in critical care meta-analysis - funnel plots, risk estimates, types of heterogeneity, baseline risk and the ecologic fallacy. Critical Care 2008; 12:220-227

23. Hunink M, Glasziou P. (2006) *Decision making in health and medicine*. 5th ed. Cambridge: Cambridge University Press

24. Koerkamp BG, Weinstein MC, Stijnen T, Heijenbrok-Kal MH, Hunink MGM. Uncertainty and patient heterogeneity in medical decision models. Med Decis Making 2010; 30:194-205

25. Braithwaite RS, Roberts MS, Justice AC. Incorporating quality of evidence into decision analytic modeling. Ann Intern Med 2007; 146:133-141

26. Koerkamp BG, Stijnen T, Weinstein MC, Hunink MGM. The combined analysis of uncertainty and patient heterogeneity in medical decision models. Med Decis Making 2010; published online 25 October 2010, http://mdm.sagepub.com/content/early/2010/10/14/0272989X10381282

27. Briggs AH. Handling uncertainty in cost-effectiveness models. Pharmacoeconomics 2000; 17:479-500

28. Nuijten MJC. Incorporation of statistical uncertainty in health economic modelling studies using second-order Monte Carlo simulations. Pharmacoeconomics 2004; 22:759-769

29. Ades AE, Claxton K, Sculpher M. Evidence synthesis, parameter correlation and probabilistic sensitivity analysis. Health Econ 2006; 15:373-381

30. Hazen GB, Huang M. Large-sample bayesian posterior distributions for probabilistic sensitivity analysis. Med Decis Making 2006; 26:512-534

31. Claxton K, Sculpher M, McCabe C, Briggs A, Akehurst R, Buxton M, et al. Probabilistic sensitivity analysis for NICE technology assessment: not an optional extra. Health Econ 2005; 14:339-347

32. Greenland S. Multiple-bias modelling for analysis of observational data. J. R. Statist Soc A 2005; 168:1-25.

33. Eddy DM, Hasselblad V, Shachter R. An introduction to a bayesian method for meta-analysis: the confidence profile method. Med Decis Making 1990; 10:15-23.

34. Shannon KM, Keith JF, Mentzer WC, Ehrenkranz RA, Brown MS, Widness JA, et al. Recombinant human erythropoietin stimulates erythropoiesis and reduces erythrocyte transfusions in very low birth weight preterm infants. Pediatrics 1995; 95:1-8.

35. Maier RF, Obladen M, Muller-Hansen I, Kattner E, Merz U, Arlettaz R, et al. Early treatment with erythropoietin beta ameliorates anemia and reduces transfusion requirements in infants with birth weights below 1000 g. J Pediatr 2002; 141:8-15.

36. Pollak A, Hayde M, Hayn M, Herkner K, Lombard KA, Lubec G et al. Effect of intravenous iron supplementation on erythropoiesis in erythropoietin-treated premature infants. Pediatrics 2001; 107: 78-85.

37. Al-Kharfy T, Smyth JA, Wadsworth L, Kyrstal G, Fitzgerald C, Davis J, et al. Erythropoietin therapy in neonates at risk of having bronchopulmonary dysplasia and requiring multiple transfusions. J Pediatr 1996; 129:89-96.

38. Juul SE. Enterally dosed recombinant human erythropoietin does not stimulate erythropoiesis in neonates. J Pediatr 2003; 143:321-326.

39. Donato H, Rendo P, Vivas R, Schvartzman G, Digregorio J, Vain N. Recombinant human erythropoietin in the treatment of anemia of prematurity: a randomized, double-blind, placebo-controlled trial comparing three doses. Int J Pediatric Hematology/Oncology 1996; 3:279-285.

40. Haiden N, Schwindt J, Cardona F, Berger A, Klebermass K, Wald M, et al. Effects of a combined therapy of erythropoietin, iron, folate, and Vitamin B12 on the transfusion requirements of extremely low birth weight infants. Pediatrics 2006; 118(5):2004-2013.

41. Birenbaum HJ, Pane MA, Helou SM, Starr KP. Comparison of a restricted transfusion schedule with erythropoietin therapy versus a restricted transfusion schedule alone in very low birth weight premature infants. Southern Med J 2006; 99(10):1059-1062.

42. Josephson CD, Wesolowski A, Bao G, Sola-Visner MC, Dudell G, Castillejo MI, et al. Do red cell transfusions increase the risk of necrotizing enterocolitis in premature infants? J Pediatr 2010; 157:972-978.

43. Blau J, Calo JM, Dozor D, Sutton M, Alpan G, La Gamma EF. Transfusion-related acute gut injury: necrotizing enterocolitis in very low birth weight neonates after packed red blood cell transfusion. J Pediatr 2011; 158:403-409.

44. Paul DA, Mackley A, Novitsky A, Zhao Y, Brooks A, Locke RG. Increased odds of necrotizing enterocolitis after transfusion of red blood cells in premature infants. Pediatrics 2011; 127:635-641.

45. Vermont Oxford Network. Key performance measures 2009. Available from: http://www.vtoxford.org

46. Maier R, Obladen M, Kattner E, Natzscha J, Messer J, Regazzoni BM, et al. High- versus low-dose erythropoietin in extremely low birth weight infants. The European multicenter rhEPO study group. J Pediatr 1998; 132(5): 866-870.

47. Meyer MP, Meyer JH, Commerford A, Hann FM, Sive AA, Moller G, et al. Recombinant human erythropoietin in the treatment of the anemia of prematurity: results of a double-blind, placebo-controlled study. Pediatrics 1994; 93:918-923.

48. Franz AR, Pohlandt F. Red blood cell transfusions in very and extremely low birth weight infants under restrictive transfusion guidelines: is exogenous erythropoietin necessary? Arch Dis Child Fetal Neonatal Ed 2001; 84:96-100.

49. Mainie P. Is there a role for erythropoietin in neonatal medicine. Early Human Dev 2008; 84:525-532.

50. Akisu M, Tuzun M, Arslanoglu S, Yalaz M, Kultursay N. Effect of recombinant human erythropoietin administration on lipid peroxidation and antioxidant enzyme(s) activities in preterm infants. Acta Med Okayama 2001; 55:357-362.

51. Atasay B, Gunlemez A, Akar N, Arsan S. Does early erythropoietin therapy decrease transfusions in anemia of prematurity. Indian J Pediatr 2002; 69(5): 389-391.

52. Bader D, Blondheim O, Jonas R, Admoni O, Abend-Winge M, Reich D, et al. Decreased ferritin levels, despite iron supplementation, during erythropoietin therapy in anaemia of prematurity. Acta Paediatrica 1996; 85:496-501.

53. Bechensteen AG, Hågå P, Halvorsen S, Whitelaw A, Liestøl K, Lindemann R et al. Erythropoietin, protein, and iron supplementation and the prevention of anaemia of prematurity. Arch Dis Child 1993; 69:19-23.

54. Chen JY, Wu TS, Chanlai. Recombinant human erythropoietin in the treatment of anemia of prematurity. Amer J Perinatol 1995; 12(5):314-318.

55. Corona G, Fulia F, Liotta C, Barberi I. Clinical use of recombinant human erythropoietin (rHuEPO) in the treatment of preterm anaemia. Rivista Italiana Pediatrica 1998; 24:442-449.

56. Emmerson AJ, Coles HJ, Stern CMM, Pearson TC. Double blind trial of recombinant human erythropoietin in preterm infants. Arch Dis Child 1993; 68:291-296.

57. Giannakopoulou C, Bolonaki I, Stiakaki E, Dimitriou H, Galanaki H, Hatzidaki E, et al. Erythropoietin (rHuEPO) administration to premature infants for the treatment of their anemia. Pediatric Hematology Oncology 1998; 15:37-43.

58. Griffiths G, Lall R, Chatfield S, Short A, Mackay P, Williamson P, et al. Randomised controlled double blind study of role of recombinant erythropoietin in the prevention of chronic lung disease. Arch Dis Child 1997; 76:F190-F192.

59. Javier MG, Natal PA, Coroleu LW, Zuasnabar CA, Badia BJ, Junca PJ, et al. Randomized multi-centre trial of the administration of erythropoietin in anemia of prematurity. Anales espanoles de pediatria 1997; 46:587-592.

60. Kivivuori SM, Virtanen M, Raivio KO, Viinikka L, Siimes MA. Oral iron is sufficient for erythropoietin treatment of very low birth-weight infants. Eur J Pediatr 1999; 158:147-151.

61. Kumar P, Shankaran S, Krishnan RG. recombinant human erythropoietin therapy for treatment of anemia of prematurity in very low birth weight infants: a randomized, double-blind, placebo-controlled trial. J Perinatol 1998; 18:173-177.

62. Reiter PD, Rosenberg AA, Valuck R, Novak K. Effect of short-term erythropoietin therapy in anemic premature infants. J Perinatol 2005; 25:125-129.

63. Rocha VLL, Benjamin ACW, Procianoy RS. The effect of recombinant erythropoietin on the treatment of anemia of prematurity. J Pediatr (Rio J) 2001; 77(2):75-83.

64. Ronnestad A, Moe PJ, Breivik N. Enhancement of erythropoeisis by erythropoietin, bovine protein and energy fortified mother's milk during anaemia of prematurity. Acta Pediatrica 1995; 84:809-811.

65. Samanci N, Ovali F, Dagoglu T. Effects of recombinant human in infants with very low birth weights. J Int Med Res 1996; 24:190-198.

66. Shannon KM, Mentzer WC, Abels RI, Freeman P, Newton N, Thompson D, et al. Recombinant human erythropoietin in the anemia of prematurity: results of a placebo-controlled pilot study. J Pediatr 1991; 118:949-955.

67. Shannon KM, Mentzer WC, Abels RI, Wertz M, Thayer-Moriyama J, Li WY, et al. Enhancement of erythropoiesis by recombinant human erythropoietin in low birth weight infants: a pilot study. J Pediatr 1992; 120:586-592.

68. Whitehall JS, Patole SK, Campbell P. Recombinant human erythropoietin in anemia of prematurity. Indian Pediatrics 1999; 36:17-27.

69. Yamada M, Takahashi R, Chiba Y, Ito T, Nakae S. Effects of recombinant human erythropoietin in infants with anemia of prematurity. I. results in infants with birth weights between 1000 and 1499 gm. Acta Neonatologica Japonica 1994; 35:755-761

70. Yamada M, Takahashi R, Chiba Y, Ito T, Nakae S. Effects of recombinant human erythropoietin in infants with anemia of prematurity. II. results in infants with birth weights between 500 and 999 gm. Acta Neonatologica Japonica 1994; 35:762-767

71. Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

72. Singer ME. Advanced Sensitivity Analyses: Probabilistic, Correlated and Scenario. July 26, 2006. Available from: http://www.hsrd.research.va.gov/for_researchers/cyber_seminars/archives/Slides_Singer.ppt

73. Shaw JW, Zachry WM. Application of probabilistic sensitivity analysis in decision analytic modeling. Formulary 2002; 37:32-40.

74. Roberts D. Normal Distribution. Oswego City School District Regents Prep Center. Available from: http://www.regentsprep.org/Regents/math/algtrig/ATS2/NormalLesson.htm

75. Stamer Sl. Current risks of transfusion-transmitted agents. A review. Arch Pathol Lab Med 2007; 131:702-707.

76. Halfhill TR. Tom's Inflation Calculator, version 7.5.2. Available from: http://www.halfhill.com/inflation.html

77. Jackson KM, Scott KE, Zivin JG, Bateman DA, Flynn JT, Keenan JD, et al. Cost-utility analysis of telemedicine and ophthalmoscopy for retinopathy of prematurity management. Arch Ophthalmol 2008; 126:493-499.

78. Vitale MG, Roye BD, Ruchelsman DE, Roye DR. Preoperative use of recombinant human erythropoietin in pediatric orthopedics: a decision model for long-term outcomes. Spine J 2007; 7:292-300.

79. Wilson LS, Basu R, Christenson M, Hensic L, Paoli C, Wara D, et al. Pediatric HIV costs across three treatment eras from 1986 to 2007. Pediatrics 2010; 126:e541-e549.

80. Bisquera JA, Cooper TR, Berseth CL. Impact of necrotizing enterocolitis on length of stay and hospital charges in very low birth weight infants. Pediatrics 2002; 109:423-428.

81. Texas Hospital Prices Revealed. Hospital Victims Project, 2004-2008. Available from: http://www.hospitalvictims.com/hv_hosp_main.asp?mpn=453304.

82. Brown GC, Brown MM, Sharma S, Tasman W, Brown HC. Cost-effectiveness of treatment for threshold retinopathy of prematurity. Pediatrics 1999; 104:e47-e52.

83. Mrus JM, Goldie SJ, Weinstein MC, Tsevat J. The cost-effectiveness of elective Cesarean delivery for HIV-infected women with detectable HIV RNA during the pregnancy. AIDS 2000; 14:2543-2552.

84. Holtgrave DR, Pinkerton SD. Updates of costs of illness and quality of life estimates for use in economic evaluations of HIV prevention programs. J Acquir Immune Defic Syndr Hum Retrovirol 1997; 16:54-62.

85. Lopushinsky SR, Fowler RA, Kulkarni GS, Fecteau AH, Grant DR, Wales PW. The optimal timing of intestinal transplantation for children with intestinal failure. A Markov analysis. Ann Surg 2007; 246:1092-1099.

86. Lorch SA, Cnaan A, Barnhart K. Cost-effectiveness of inhaled nitric oxide for the management of persistent pulmonary hypertension of the newborn. Pediatrics 2004; 114:417-426.

87. MacLaren R, Sullivan PW. Cost-effectiveness of recombinant human erythropoietin for reducing red blood cells transfusions in critically ill patients. Value Health 2005; 8:105-116.

88. Higgins JPT. Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003; 327:557-560.

89. Shermock KM, Horn E, Lipsett PA, Pronovost PJ, Dorman T. Number needed to treat and cost of recombinant human erythropoietin to avoid one transfusion-related adverse event in critically ill patients. Crit Care Med 2005; 33:497-503.

90. Abdullah F, Zhang Y, Camp M, Mukherjee D, Gabre-Kidan A, Colombani PM, et al. Necrotizing enterocolitis in 20822 infants: analysis of medical and surgical treatments. Clin Pediatr 2010; 49:166-171.

91. Sinha M, Das A. Cost effectiveness analysis of different strategies of management of chronic hepatitis C infection in children. Pediatr Infect Dis J 2000; 19:23-30.

TABLES

Table 1. Trials of late r-Epo treatment and assessment of quality of trial evidence

Trial	n	Gest age (wk)	Birth weight (g)	Trial Design	Epo dose	Iron dose	Transfusion Policy	Design Quality Level	Int Validity	Ext Validity
Akisu 2001	40	≤ 32	< 1500	RCT	High	Low	None	2.1	Poor	Low
Al Kharfy 1996	55	26.5 mean	< 1250	RCT	High	High	Strict	1	Good	High
Atasay 2002	27	< 32	< 1500	RCT	High	Low	Liberal	2.1	Poor	Low
Bader 1996	29	< 34	< 1750	RCT	High	High	Liberal	2.1	Poor	Low
Bechensteen 1993	29		900-1400	RCT	Low	High	Liberal	2.1	Poor	Low
Chen 1995	70	≤ 33	≤ 1750	RCT	Low	Low	Liberal	2.1	Poor	Low
Corona 1998	60	≤ 32	< 1500	RCT	Low	Low	Liberal	2.1	Poor	Low
Emmerson 1993	24	30 mean		RCT	Low	Low	Strict	1	Poor	Low
Giannakopoulou 1998	68		< 1300	RCT	High	High	Liberal	2.1	Poor	Low
Griffiths 1997	42	≤ 32	≤ 1500	RCT	Low	Low	Strict	1	Poor	Low
Javier 1997	28	< 34		RCT	High	Low	?	2.1	Poor	Low
Kivivuori 1999	41	29-30 mean	< 1500	RCT	High	High	Liberal	2.1	Poor	Low
Kumar 1998	30	< 32	< 1250	RCT	High	High	Strict	2.1	Fair	High
Maier 2002	145*	< 30	< 1000	RCT	High	High	Strict	1	Good	High
Meyer 1994	80	≤ 32	≤ 1500	RCT	High	High	Strict	1	Good	High
Pollack 2001	38	< 31	< 1300	RCT	High	High	Strict	2.1	Poor	Low
Reiter 2005	60	< 32	1814-1909	RCT	High	High	Strict	2.1	Fair	High
Rocha 2001	42	≤ 32	< 1550	CT	High	High	Strict	2.1	Poor	Low
Ronnestad 1995	24	< 32		RCT	Low	Low	Liberal	1	Poor	Low
Samanci 1996	24	≤ 32	≤ 1250	RCT	High	Low	Strict	1	Fair	Low
Shannon 1991	20	< 34	≤ 1250	RCT	Low	Low	Strict	1	Fair	Low
Shannon 1992	8	≤ 32	< 1250	RCT	High	High	Strict	1	Fair	High
Shannon 1995	157	< 31	≤ 1250	RCT	High	High	Strict	1	Good	High
Whitehall 1999	42	≤ 32	≤ 1000 vs 1001-1400	RCT	High	High	Strict	2.1	Fair	High
Yamada 1994 (parts I and II)	82	≤ 32	< 1500	RCT	Low	Low	?	2.1	Poor	Low
Shah 2010 #	85	28 mean	< 1500	Case control	High	High	Strict	2.2	Poor	Low
Birenbaum 2006 #	50	< 30	< 1500	Time series	High	High	Strict	2.3	Poor	Low

* = number with late r-Epo treatment. Design Quality level 1=RCT, 2.1 = controlled trial, 2.2=case/control, 2.3=cohort/times series, 3= expert opinion

= ? timing of r-Epo treatment

Table 2. Comments on quality scoring for late r-Epo treatment trials and transfusion risk parameter

Trial	Comments
Akisu 2001	design = not blinded, 1 center; Poor int./low ext. validity = no transfusion guidelines, low iron dose
Al Kharfy 1996	single center RCT, int. and ext validity good
Atasay 2002	design = not adequately blinded; Poor int./low ext. validity = control group had no iron treatment, low iron dose, small sample size
Bader 1996	design = not adequately blinded; Poor int./ext validity = liberal transfusion, small sample size
Bechensteen 1993	design = not adequately blinded, single center; Poor int./ext validity = liberal transfusion , low rEpo, small sample size
Chen 1995	design = not adequately blinded; Poor int./low ext. validity = low rEpo and iron dose, liberal transfusion
Corona 1998	design = not adequately blinded, single center; Poor int./low ext. validity = low rEpo and iron dose, liberal transfusion
Emmerson 1993	single center RCT, Poor int./low ext. validity = low rEpo and iron dose, combined all r-Epo dosing groups for analysis, small sample size
Giannakopoulou 1998	design = not adequately blinded; Poor int./low ext. validity = liberal transfusion
Griffiths 1997	multicenter RCT; Poor int./low ext. validity= ventilated only patients, stopped enrollment early lack recruitment, low r-Epo and low iron dose, excluded deaths in analysis
Javier 1997	design = not adequately blinded; Poor int./low ext. validity = no iron dose for controls, no comment on transfusion guidelines, small sample size
Kivivuori 1999	design = not blinded; Poor int./low ext. validity = liberal transfusion, IM dosing of iron in 2 of 3 groups; excluded > 10% of randomized
Kumar 1998	single center, sample size, ? blinding of treatment allocation, mismatched gestational age in groups
Maier 2002	multicenter RCT, int. and ext validity good; had early r-Epo group, but also late r-Epo group and control; satellite pack blood bank to reduce donor exposure, restricted to <1000 g infants, weaker statistical analysis
Meyer 1994	multicenter RCT, int. and ext validity good, included deaths in analysis, enrolled larger, healthier preterm infants unlike other high quality r-Epo trials
Pollack 2001	design = not blinded; Poor int./low ext. validity= removal of transfused from analysis (disqualified 25%), IV iron, ? selective reporting, groups not balanced
Reiter 2005	10 day course; design = not adequately blinded, single center; crossover of treatment after initial 10 days
Rocha 2001	design = not blinded, not randomized, single center; Poor int./low ext. validity= delay of iron dose until 30 d unlike treatment group, sample size not calculated until after start of trial, and then stop trial after 50% enrollment, reports mean transfusions but no standard deviation
Ronnestad 1995	RCT, single center; Poor int./low ext. validity= low iron and r-Epo dose, liberal transfusion, small sample size
Samanci 1996	RCT, single center; Fair int./low ext. validity= low iron, excluded prior transfused infants, small sample size
Shannon 1991	RCT, single center; Fair int./low ext. validity= small sample size, low iron and r-Epo dose, large blood drawn out in groups
Shannon 1992	RCT, single center; Fair int. validity= small sample size (pilot trial)
Shannon 1995	multicenter RCT, int. and ext validity good

Whitehall 1999	10 day course; design = not blinded, single center; Fair int./high ext. validity= sample size; no mention of proportions requiring transfusion, less statistical precision
Yamada 1994 (parts I and II)	design = not blinded, single center; Poor int./low ext. validity= low iron and r-Epo dose, unclear transfusion policy;
Shah 2010	10 day course; design = case control, Poor int./low ext. validity= not case/control matched adequately, excluded deaths and infants taken off r-Epo for sepsis in analysis, ? timing of dosing of r-Epo;
Birenbaum 2006	10 day course; design = time series, single site; Poor int./low ext. validity= confounders not addressed, ? timing of dosing of r-Epo, IV iron, excluded deaths in analysis

Table 3. Studies of association of necrotizing enterocolitis and blood transfusion and quality of evidence

Study	n	Birth Weight (g)	Trial Design	Confounders addressed	Design Quality Level	Int Validity	Ext Validity	Comment
Mally 2006	17	< 32	cohort	No	2.3	Poor	High	sample size, 1 center, cohort not matched-confounder
Josephson 2010	184	< 34	case control	Yes	2.2	Good	High	multicenter. well matched
Christensen 2010	310	< 32	case control	Yes	2.2	Good	High	multicenter, well matched
Blau 2011	36	<1500	cohort	No	2.3	Poor	Low	sample size, 1 center, included gest age > 34 weeks, cohorts mismatched - confounder
Paul 2011	122	<1500	cohort	No	2.3	Poor	High	1 center, cohort mismatched-confounder

Table 4. Medical decision model risk parameters with distributions used in probabilistic sensitivity analysis.

PARAMETER [source]	VALUE	DISTRIBUTION*
Probabilities		
Long course: r-Epo		
Probability of transfusions ** [34, 37]	0.741 ± 0.052	Beta (α = 52.895, β=18.513)
Probability of transfusions with r-Epo** [34, 37]	0.548 ± 0.023	Beta (α = 267.575, β=220.701)
Number of transfusions/infant ** [34, 37]	2.66 ± 2.59	Normal (2.66, 2.59)
Number of transfusions/infant with r-Epo** [34, 37]	1.72 ± 1.84	Normal (1.72, 1.84)
Short course: r-Epo		
Probability of transfusions [62]	0.1	Uniform (0.05, 1.5)
Probability of transfusions with r-Epo [62]	0.033	Uniform (0.0166, 0.05)
Number of transfusions/infant [62]	0.27 ± 1.11	Uniform (0.135, 0.405)
Number of transfusions/infant with r-Epo [62]	0.067 ± 0.37	Uniform (0.0335, 0.105)
Acute hemolytic transfusion reaction [78, 89]	0.112E-04 - 2.0E-04	Uniform (0.112E-04, 2.0E-04)
Acute hemolytic transfusion reaction mortality [78]	9.8E-03	Uniform (0.0049, 0.0147)
Transfusion acquired Hepatitis (B or C) infection [75]	3.98E-06 (2.56E-06 - 5.4E-06)	Beta(α = 31.668, β=7956743.84)
Transfusion acquired HIV infection [75]	4.68E-07 (2.3E-07 - 9.4E-07)	Beta (α = 6.95176, β=14845180.69)
NEC <1500 g birth weight [45]	0.06 [2.7 Q1, 8.1 Q3]	Beta (α = 2.055, β=32.195)
Odds ratio NEC following transfusion [5, 42]	0.73 to 11.7	Uniform (0.73, 11.7)
NEC <1500 g birth weight after transfusion	[(ORNEC)(pNEC)/(1-pNEC)] / [((ORNEC)(pNEC)/(1-pNEC))+1]	
Proportion with Surgical NEC [90]	0.26	Uniform (0.13, 0.39)
Proportion with Medical NEC [90]	1 - pSurgical NEC	
Surgical NEC mortality [90]	0.308	Uniform (0.154, 0.462)
Medical NEC mortality [90]	0.067	Uniform (0.034, 0.1)
Severe ROP with laser < 1500 g birth weight [45]	0.063 [1.6 Q1, 8.9 Q3]	Beta (α=1.3693, β=19.0679)
Relative risk of severe ROP with laser after r-Epo [7]	0.83 (0.23, 2.98) 95% CI	Uniform (0.23, 2.98)
Severe ROP with laser < 1500 g after r-Epo	(RR ROP r-Epo)*(pROP)	

r-Epo = erythropoietin, NEC = necrotizing enterocolitis, ROP = retinopathy of prematurity
* Distribution parameters: Beta (α , β); Normal (mean, SD), Uniform (low, high)
** Pooled estimate

Table 5. Decision model cost and utility parameters with distributions for probabilistic sensitivity analysis.

PARAMETER [source]	VALUE	DISTRIBUTION*
Costs		
r-Epo treatment - long course (18 doses) [10]	$828.31	Uniform (414.15, 1242.47)
r-Epo treatment - short course (10 doses) [10]	$267.11	Uniform (138.06, 414.17)
Cost/transfusion [10]	$283.66	Uniform (141.83, 425.49)
Total cost of all transfusions	(cost per transfusion) * (# transfusions)	
Chronic hepatitis (B or C) /year** [78]	$2503.86	Uniform (1251.00, 3455.79)
HIV infection / year [79]	$25,147.68	Uniform (12,573.84, 37721.52)
Severe ROP with laser [77]	$1448.00	Uniform (724.00, 2172.00)
Non-fatal transfusion reaction [87]	$2531.84	Uniform (1265.92, 3797.76)
Cost hospitalization baseline (non-NEC) survivor [80]	$192,702.55	Uniform (96,351.28, 289053.83)
Cost hospitalization baseline (non-NEC) non-survivor[80]	$138,466.45	Uniform (69,233.23, 207,699.68)
Cost hospitalization with fatal transfusion reaction	Use cost hospitalization for non-NEC non-survivor	Uniform (69,233.23, 207,699.68)
Cost hospitalization medical NEC survivor [80]	$240,223.87	Uniform (120,111.94, 360,335.81)
Cost hospitalization medical NEC non-survivor [80]	$161,535.23	Uniform (80,767.62, 242,302.85)
Cost hospitalization surgical NEC survivor [80]	$354,271.68	Uniform (177,135.84, 531,407.52)
Cost hospitalization surgical NEC non-survivor [80]	$127,706.24	Uniform (63,853.12, 191,559.36)
Utilities		
Medical NEC survivor, adapted using [86]	0.935	Uniform (0.87, 1.0)
Surgical NEC survivor, adapted using [85]	0.85 (0.8 - 0.95)	Uniform (0.8, 0.95)
Severe ROP with laser [77, 82]	0.704 (0.7 - 0.89)	Uniform (0.7, 0.89)
HIV during 1st year [83, 84]	0.65 (0.59 - 0.76)	Uniform (0.59, 0.76)
Chronic Hepatitis 1st year [78]	0.9 (0.82 - 1.0)	Uniform (0.82, 1.0)

r-Epo = erythropoietin, ROP = retinopathy of prematurity, NEC = necrotizing enterocolitis
r-Epo = erythropoietin, NEC = necrotizing enterocolitis, ROP = retinopathy of prematurity
* Distribution parameters: Beta (α , β); Normal (mean, SD), Uniform (low, high)
** Pooled estimate

Table 6. Probabilistic sensitivity analysis mean estimates of cost-effectiveness for long course (6 weeks), and short course (10 days) of recombinant Erythropoietin (r-Epo).

Strategy	Cost	Incremental Cost	Effectiveness QALY	Incremental Effectiveness QALY	Cost-Effectiveness	Incremental Cost-Effectiveness
Long r-Epo Course						
No r-Epo	$205,824.37		0.94875		216942.68	
r-Epo	$206,470.94	$646.57	0.94076	-0.00799	219472.49	Dominated
Short r-Epo Course						
No r-Epo	$198869.41		0.9721		204577.11	
r-Epo	$199198.95	$329.54	0.9639	-0.0082	206659.35	Dominated

FIGURES

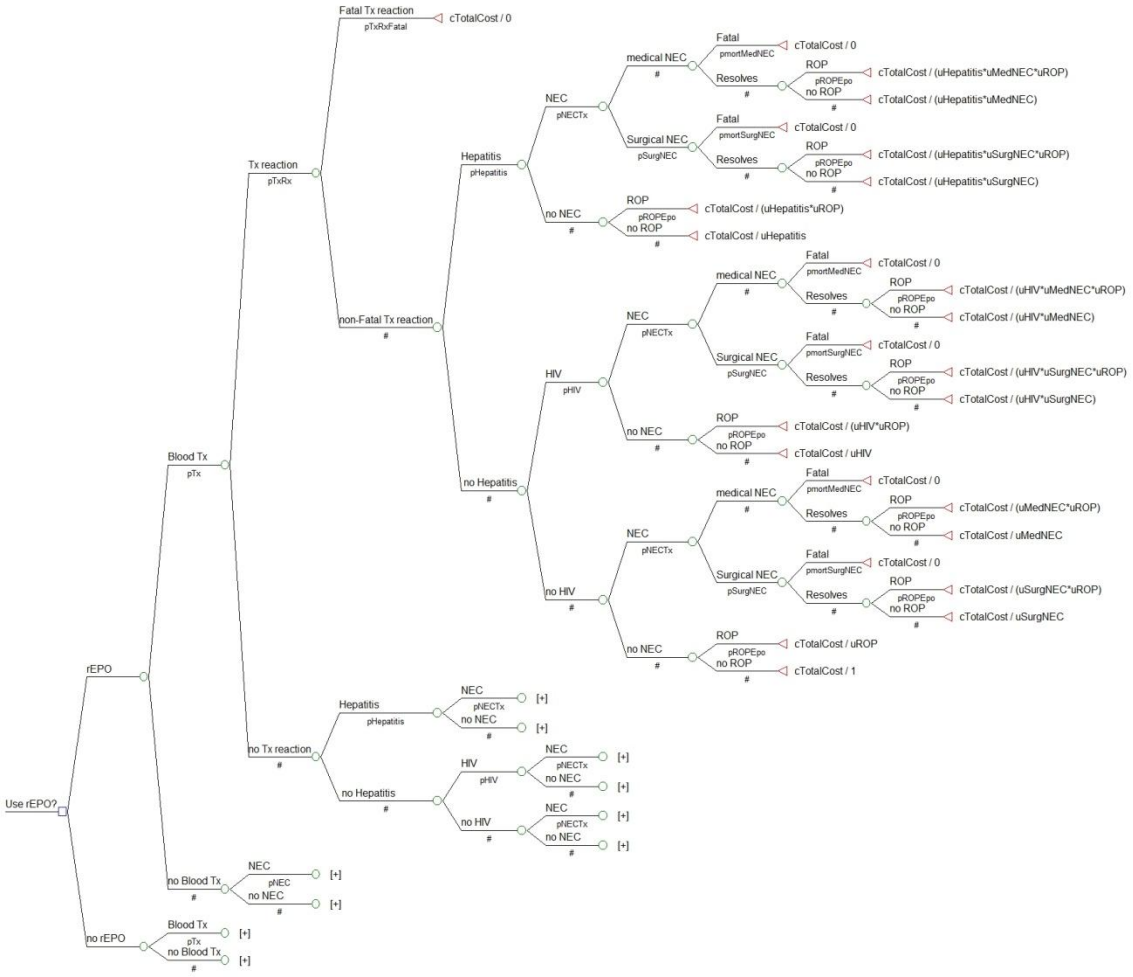

Figure 1. Medical decision model for use of erythropoietin in premature infants.

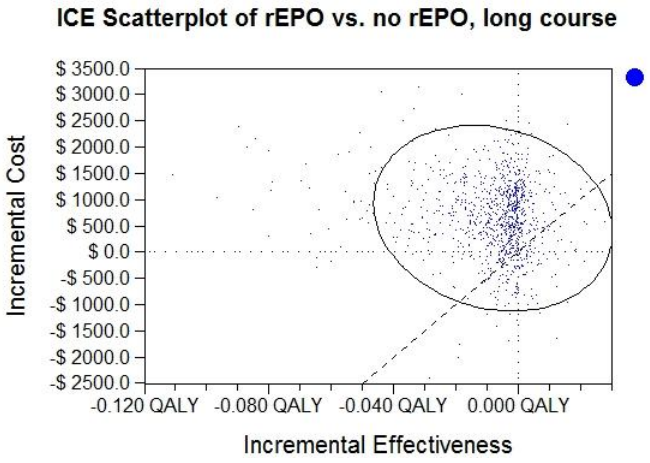

Figure 2. Incremental Cost-Effectiveness Scatter plot for r-Epo long course. Willingness-to-pay = $50,000.

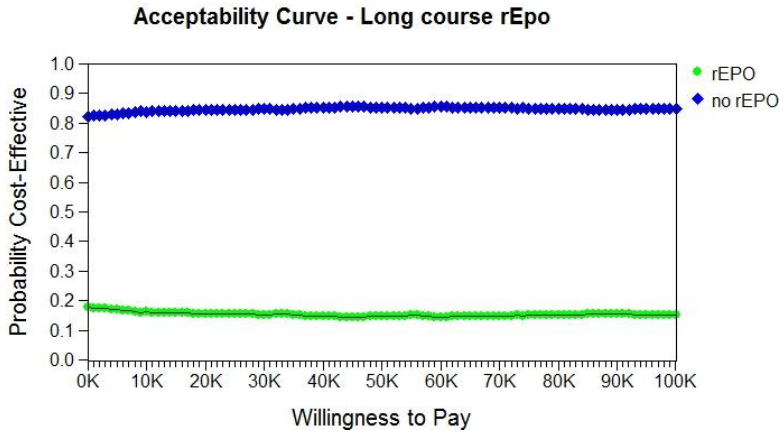

Figure 3. Acceptability curve for r-Epo long course.

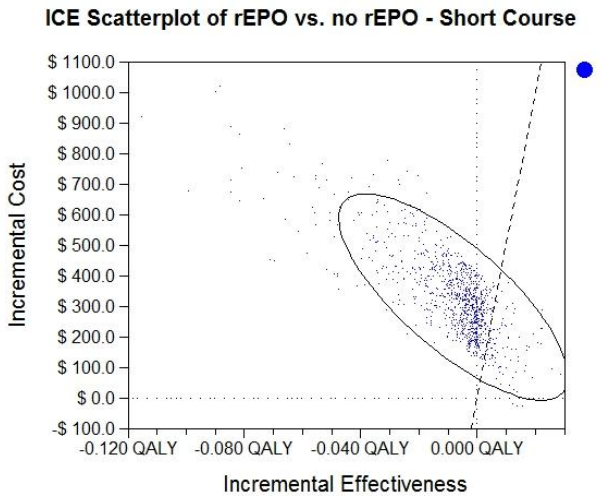

Figure 4. Incremental Cost-Effectiveness Scatter plot for r-Epo short course. Willingness-to-pay = $50,000.

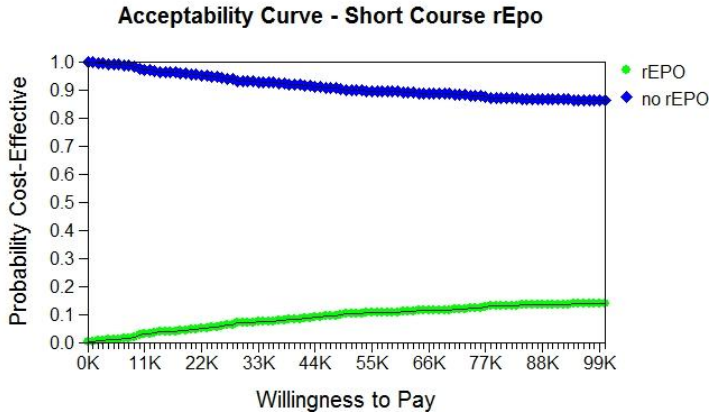

Figure 5. Acceptability curve for r-Epo short course.