Cost-effectiveness of continuous erythropoietin receptor activator in anemia

Holger Schmid1,2
1Clinic and Policlinic IV, Section of Nephrology, Munich University Hospital, Campus Innenstadt, Munich, Germany; 2KfH Nierenzentrum Muenchen Laim, Munich, Germany

Background: Erythropoiesis-stimulating agents (ESAs) are the mainstay of anemia therapy. Continuous erythropoietin receptor activator (CERA) is a highly effective, long-acting ESA developed for once-monthly dosing. A multitude of clinical studies has evaluated the safety and efficiency of this treatment option for patients with renal anemia. In times of permanent financial pressure on health care systems, the cost-effectiveness of CERA should be of particular importance for payers and clinicians.

Objective: To critically analyze, from the nephrologists’ point of view, the published literature focusing on the cost-effectiveness of CERA for anemia treatment.

Methods: The detailed literature search covered electronic databases including MEDLINE, PubMed, and Embase, as well as international conference abstract databases.

Results: Peer-reviewed literature analyzing the definite cost-effectiveness of CERA is scarce, and most of the available data originate from conference abstracts. Identified data are restricted to the treatment of anemia due to chronic kidney disease. Although the majority of studies suggest a considerable cost advantage for CERA, the published literature cannot easily be compared. While time and motion studies clearly indicate that a switch to CERA could minimize health care staff time in dialysis units, the results of studies comparing direct costs are more ambivalent, potentially reflecting the differences between health care systems and variability between centers.

Conclusion: Analyzed data are predominantly insufficient; they miss clear evidence and have to thus be interpreted with great caution. In this day and age of financial restraints, results from well-designed, head-to-head studies with clearly defined endpoints have to prove whether CERA therapy can achieve cost savings without compromising anemia management.

Keywords: CERA, erythropoietin, anemia, cost, cost-effectiveness

Background

Anemia is associated with reduced quality of life, significant morbidity, and increased mortality.1 Partial correction of anemia, the maintenance of stable hemoglobin (Hb) levels, and a reduced frequency of therapeutic interventions are common goals in anemia therapy.2,3 Besides treatment of underlying diseases and compensation of iron, vitamin B12, or folate deficiencies, red blood cell (RBC) transfusions were traditionally used for the correction of anemia.4 The introduction of erythropoiesis-stimulating agents (ESAs) more than two decades ago has often nearly completely replaced donation of RBC transfusions.5 Today, the two major therapeutic areas for ESA treatment are anemia associated with chronic kidney disease (CKD) and anemia due to chemotherapy in cancer patients.6,7 Different ESA types currently available in the European Union (EU) are summarized in Table 1.
Table 1 Selection of ESAs, excluding “biosimilars”, which are currently available in the EU

| ESA class       | ESA type            | Marketed as, for example (company) | Molecular weight (KDa) | Serum half-life (hours)/route of administration | Bioavailability (%) | Periodicity of administration | MSP* for prefilled syringes |
|-----------------|---------------------|------------------------------------|------------------------|-----------------------------------------------|--------------------|--------------------------------|-------------------------------|
| Unmodified recombinant rhuEPOs (“short-acting” ESA) | Epoetin alpha        | Procrit® (Johnson & Johnson, New Brunswick, NJ, USA), Epogen® (Amgen Inc., Thousand Oaks, CA, USA), Erypo® FS (Janssen-Cilag; Johnson & Johnson) | 32–40                  | 8.8/IV 24.2/SC                               | 30%–36%            | 1–3 times/week                  | 6 PS 4.000 IE €199             |
|                 | Epoetin beta        | NeoRecormon® (Hoffman-La Roche Ltd, Basel, Switzerland) | 6.8/IV 19.4/SC         | 23%–42%                                      |                    | 1–3 times/week                  | 6 PS 4.000 IE €199             |
| “Long-acting” ESAs | Darbepoetin alpha   | Aranesp® (Amgen Inc.)               | 40                     | 25/IV 49/SC                                  | 37%                | Every 1–2 weeks                  | 4 PS 40 μg €385                |
|                 | CERA                | Micrera® (Hoffman-La Roche Ltd)     | 60                     | 133/IV 137/SC                                | 47%–52%            | Every 2–4 weeks                  | 3 PS 75 μg/0.3 mL €606         |

Notes: *MSPs correspond to published prices in Germany in 2013. Epoetin beta and CERA are not licensed in the United States.

Abbreviations: ESA, erythropoiesis-stimulating agent; EU, European Union; MSP, market sales price; rhuEPOs, recombinant human erythropoietins; IV, intravenous; SC, subcutaneous; PS, prefilled syringes; IE, international equivalents; CERA, continuous erythropoietin receptor activator.

Although ESA therapy can often result in dramatic benefits initially, long-term improvement in outcomes is disappointing, particularly in patients with CKD or end-stage renal disease. Furthermore, randomized controlled trials in CKD patients not on dialysis, with or without diabetes, resulted in serious concerns about the safety of ESA therapy. In addition to more cautious and individualized ESA use, current trends in anemia management mainly focus on simplifying and economizing ESA treatment, as this kind of treatment still generates significant costs.

The pegylated erythropoietin continuous erythropoiesis receptor activator (CERA) (methoxy polyethylene glycol-epoetin beta; Micrera®; Hoffman-La Roche Ltd, Basel, Switzerland) has a unique erythropoietin receptor binding kinetic, allowing for once-a-month dosing. CERA has been extensively tested in preclinical and clinical studies. In CKD patients, the safety profile of CERA and its efficacy – as compared to that of other ESAs, including the longer acting ESA analog, darbepoetin alfa (DA) (Aranesp®; Amgen Inc., Thousand Oaks, CA, USA) – was not always convincing. In advanced non-small-cell lung cancer patients receiving chemotherapy, CERA treatment was prematurely stopped due to high mortality.

This safety signal had significant market impact, so that CERA was only approved for treatment of renal anemia by the EU in July 2007 and by the United States Food and Drug Administration (FDA) in November 2007. Patent disputes between Hoffman-La Roche Ltd, and its rival, Amgen, have prevented CERA importation into, or use in, the US until mid-2014, when patents for Amgen’s Aranesp® expire in most territories.

The incidence and prevalence of patients with anemia is growing worldwide. In view of increasing health care costs and escalating financial pressure on public and private payers, it is desirable to improve the cost-effectiveness of ESA therapy while maintaining high standards of care. Adoption of a reasonably priced ESA regimen providing predictable and stable Hb responses with minimal administration frequency should be most welcome.

Recent data already argue that the introduction of CERA could offer relevant cost savings compared to a conventional first-generation ESA (epoetin [EPO] alpha or beta) therapy: firstly, the cost-effectiveness of pegylated drugs has been indicated in various clinical settings; secondly, the nursing staff costs in particular are directly affected by the dosing frequency of the ESA; Finally, a landmark study by Schiller et al demonstrated that use of a once-monthly ESA to correct anemia in dialysis patients may provide substantial time, resource, and cost savings.

But are these findings the simple solution to this complex question: can the administration of once-monthly CERA result in cost-effectiveness or even cost savings when compared to other available ESAs? To solve this pivotal issue from the clinicians’ perspective, available data reporting the
costs associated with CERA treatment for anemia in chronic disease were critically reviewed by a nephrologist.

**Methods**

**Search strategy**

In July 2013, electronic databases including MEDLINE® (US National Library of Medicine, Bethesda, MD, USA), PubMed (National Center for Biotechnology Information, US National Library of Medicine), and Embase (Elsevier Inc., Philadelphia, PA, USA) were queried for published literature on the definite or estimated costs and cost-effectiveness of CERA for anemia treatment. Additional studies were identified by searching bibliographies of related publications and using the Google internet search engine (Google, Mountain View, CA, USA). Final updated searches were undertaken in January 2014. Iterative searches of conference abstract databases (including the International Society of Nephrology [Brussels, Belgium], the American Society of Nephrology [Washington, DC, USA], the European Renal Association–European Dialysis and Transplantation Association [Parma, Italy], the American Society of Hematology [Washington, DC, USA], the European Hematology Association [the Hague, the Netherlands], and the International Society For Pharmacoeconomics and Outcomes Research [Lawrenceville, NJ, USA]) were conducted to find relevant abstracts presented between 2008 and 2013.

The applied search terms were: “Mircera”, “methoxy polyethylene glycol epoetin-beta”, “continuous erythropoiesis receptor activator”, or “CERA”; and “anemia”, “anaemia”, “haemoglobin”, or “hemoglobin” and “cost”, “costs”, or “cost-effectiveness”.

**Study selection**

Inclusion criteria were: 1) language of publication restricted to English; 2) studies or trials relating to costs and the cost-effectiveness of CERA treatment in anemia related to CKD, cancer, or chronic heart failure; 3) studies published in peer-reviewed journals or abstracts presented at conferences of international societies; and 4) studies involving adult patients.

The exclusion criteria for this study were: 1) non-English language publications; 2) studies concentrating solely on outcomes or quality of life without any description of costs or time savings associated with CERA treatment; and 3) editorials and scholarly reviews. A flowchart of the study selection procedure is depicted in Figure 1.

From the initial search of the three selected journal databases, 36 potentially relevant abstracts were found. A further eleven abstracts were included in this initial search from cross-referencing. Searches of the conference abstract databases produced 14 additional abstracts. A total of 61 selected abstracts were reassessed and further analyzed by the author. Forty of the 61 abstracts were immediately excluded, as they did not fulfill the proposed inclusion criteria, or they were duplicates. The remaining 21 abstracts were analyzed...
for relevance, with three of these excluded as they did not directly discuss CERA-associated costs or associated time savings. Eighteen papers or abstracts were finally chosen for discussion in this review.

Results
The literature query focusing on the costs and cost-effectiveness of CERA treatment for anemia showed a relative paucity of research published to date. With respect to the different potential indications, relevant studies were restricted to patient cohorts with renal anemia.

The 18 selected studies can be divided into seven papers that were published in peer-reviewed journals and eleven meeting abstracts presented at conferences of international societies. As a matter of principle, the literature can be divided into one of the following groups: studies demonstrating an increase of costs; or studies arguing for a cost reduction associated with CERA treatment. A further subcategorization of the latter selected studies was made: studies demonstrating definite cost reduction; studies suggesting potential cost reduction; and studies suggesting time reduction leading to a subsequent reduction of costs.

Studies demonstrating increasing costs after a switch to CERA therapy are summarized in Table 2. These included one cost-effectiveness analysis (CEA), one cost-minimization analysis (CMA), and four single-center studies with predominantly small patient numbers and limited study duration of 6 months or 12 months, respectively. Of note, four of the six studies analyzed hospital-based centers. Silva et al used a CEA and Markov model to evaluate the impact of a hypothetical switch to CERA in Brazilian dialysis patients and found conventional EPO to be more cost effective for the public health system. The results were confirmed by a sensitivity analysis. Unfortunately, more detailed information regarding the treatment’s cost-effectiveness (for example, median costs/patient/month for EPO versus CERA) was not available from the abstract. A CMA conducted in two Spanish tertiary hospitals compared EPO, DA, and CERA in CKD patients.

Table 2 Studies demonstrating increased medication costs after a switch to CERA therapy

| Study | Design and setting | Patient number, type, mean age (years) | Duration (months) | Comparator ESAs and median doses | Costs |
|-------|-------------------|---------------------------------------|-------------------|---------------------------------|-------|
| Silva et al (MA) | CEA, Markov model, sensitivity analysis; PHS, Brazil | NA; D | 48 | Epo, CERA | Epo more cost-effective than CERA Costs/QALY for CERA: R $72.974 (∼€25.906) |
| Escudero-Vilaplana et al (PRJ) | CMA, multicenter, two hospitals; Spain | 409; HD, PD, pre-D | NA | Epo, DA, CERA | Median costs/patient/month Epo (€103.20) versus DA (€134.40) versus CERA (€147.50) |
| Albero Molina et al (PRJ) | Prospective, single-center, hospital; Spain | 17; HD | 6 | Epo SC, CERA SC (160±40 μg/month, month 1–5, 200±95 μg/month, month 6) | Average costs/patient/month (months 1–5): Epo (€174.30±€85.40) versus CERA (€290.10±€69.00; +66.4%) Further increase of costs for CERA at month 6: CERA (€361.60±€169.30; +107%) |
| Tsai et al (PRJ) | Retrospective, single-center, hospital; Taiwan | 15; PD; 50.4±13.1 | 6 | DA (1.51 μg/kg/month), CERA (1.59 μg/kg/month) | Costs for CERA are slightly higher (NS; P=0.156) Average costs/patient/month: DA NT ($4,337±$1,069; ∼€105±€62) versus CERA NT ($4,775±$728; ∼€115±€73) |
| Padullés-Zamora et al (PRJ) | Retrospective, single-center, hospital and outpatient clinic; Spain | 190; pre-D; 65 (range: 22–93) | 12 | Epo beta, DA, CERA (75 μg/month; range: 50–150 μg/month) | Higher costs after switching from Epo beta, but more cost effective after switching from DA Average costs/patient/month: Epo beta ($86.8) versus CERA ($135.10; P<0.001); DA ($220.10) versus CERA ($148.90; P<0.001) |
| Olmos et al (MA) | Retrospective, single-center, D center; Uruguay | 17; D; 70 (range: 47–85) | 12 | Conventional Epo (23.150 IU/month), CERA (122 μg/month) | Higher medication costs/year for conventional Epo (US $14,170; ∼€10,121) versus CERA (US $15,000; ∼€10,741) Lower total costs/year for conventional Epo (US $27,860; ∼€19,900) versus CERA (US $16,809; ∼€12,006) fewer transfusions and hospitalizations; better compliance |

Note: In order to enhance the comparability between the different studies, all currencies were translated into Euros (€).

Abbreviations: CERA, continuous erythropoietin receptor activator; ESA, erythropoiesis-stimulating agent; MA, meeting abstracts; CEA, cost-effectiveness analysis; HD, hemodialysis; PD, peritoneal dialysis; NA, not applicable; D, dialysis; Epo, epoetin; QALY, quality-adjusted life year; R, Brazilian dollar; PRJ, peer-reviewed journal; CMA, cost-minimization analysis; NA, not applicable; DA, darbepoetin alpha; SC, subcutaneous; NS, not significant; NT, Taiwan dollar.
on and not on dialysis and found the highest median costs/patient/month for CERA treatment.32

Overall, median ESA costs/patient under CERA treatment in studies demonstrating an increase in costs ranged between €115/month and €290/month. Exceptionally high average costs/patient/month of €290.1±€69.0 were demonstrated in a prospective analysis including hemodialysis (HD) patients.33 At month 6 after switching from subcutaneous EPO to subcutaneous CERA, the monthly cost/patient further increased to €361.6±€169.3. Only a slight but not significant increase in costs after switching from DA to CERA was obvious in a retrospective study that included 15 patients treated with peritoneal dialysis.34

Two studies reported a more subtle result related to different comparator ESAs or total treatment costs, respectively. In a mixed cohort of 190 predialysis patients, Padullész-Zamora et al35 found a significant increase in costs after switching from EPO beta to CERA, whereas a switch from DA to CERA was cost effective. Of particular note, when comparing the observed costs with the expected costs based on the theoretical dosage, the authors found additional possible savings. Lower doses than those recommended in the drug leaflet allowed for sufficient Hb control during the first 3 months postswitch.

Despite the higher medication costs associated with a switch from conventional EPO to CERA, the total treatment costs per patient and year were lower in a small cohort of 17 dialysis patients.36 This effect was due to fewer transfusions and hospitalizations in the CERA-treated patients. Reproducibility of these retrospective observational data is difficult, as data were obtained from a single center, and comparatively very high costs were reported for EPO in this center.

In studies demonstrating increasing costs associated with CERA therapy, median CERA doses revealed a broad variation, with average values ranging from 75–200 μg/month.33–36

Five studies37–41 demonstrating definite cost reduction with CERA compared to conventional ESA therapy are summarized in Table 3. Again, these are predominantly retrospective single-center studies including small patient numbers. Data were available from meeting abstracts alone, and to date, none of these studies was published in a peer-reviewed journal.37–41 One cannot exclude that two of the studies analyzed an identical cohort of dialysis outpatients at different time points.39,40 There is considerable variation in cost reduction, which ranges between 14%–45%,37–41 with the lowest cost reductions reported in the single prospective multicenter study.38 Compared to the studies that reported cost increases, the average CERA doses were slightly higher and varied between 92–228 μg/month; however, further assessment of the cost impact related to dosing errors was not noted in any of the cited studies.37–41

Table 3 Studies demonstrating definite cost-reduction after a switch to CERA therapy

| Study                      | Design and setting                      | Patient number, type, mean age (years) | Duration (months) | Comparator ESAs and median doses | Costs                                           |
|----------------------------|----------------------------------------|---------------------------------------|------------------|----------------------------------|------------------------------------------------|
| Muller and Moll37 (MA)      | Retrospective, single-center, D center; Germany | 26; HD; 60 (range: 46–90)             | 7                | Epo beta SC (43,000±30,923 IU/month), CERA IV, Q4w (139 μg/month) | 22.3% cost reduction/patient/month Cost savings: €113/month and €1,356/year |
| Franz et al38 (MA)          | Prospective, multicenter, 34 D centers; Switzerland | 184; HD, PD; 65 (range: 25–95)        | 6                | Epo alpha, Epo beta, DA, CERA (160 μg/month) | 14% cost reduction/patient/month Epo alpha, Epo beta, DA CHF 759 (−€506) versus CERA CHF 650 (−€433) (P=0.004) |
| Cynke et al39 (MA)          | Retrospective, single-center, D center; Switzerland | 14; D; NA                             | 15               | Epo beta (16,640 IU/week) CERA (214 μg/month) | 35% cost reduction/patient/month Epo beta CHF 1,340 (−€893) versus CERA CHF 848 (−€565) months 1–14 (CHF 802; −€533; month 15) |
| Franz and Cynke40 (MA)      | Retrospective, single-center, D center; Switzerland | 14; D; NA                             | 5                | Epo beta (16,640 IU/week), CERA (228 μg/month, months 1–4, 169 μg/month, month 5) | 45% cost reduction/patient/month Epo beta CHF 1,251 (−€782) versus CERA CHF 921 (−€576) months 1–4 (CHF 658; −€411; month 5) |
| Echarri et al41 (MA)        | Retrospective, CEA, sensitivity analysis, single-center, hospital; Spain | 38; PD; 38, 59                        | 12               | DA (137 μg/month) versus CERA (92 μg/month) | 39% cost reduction/patient/year DA (€5.440) versus €3.340 Cost savings: €2.100/patient/year |

**Note:** In order to enhance the comparability between the different studies, all currencies were translated into Euros (€).

**Abbreviations:** CERA, continuous erythropoietin receptor activator; MA, meeting abstracts; D, dialysis; HD, hemodialysis; Epo, epoetin; SC, subcutaneous; IV, intravenous; Q4w, every 4 weeks; PD, peritoneal dialysis; DA, darbepoetin alpha; CHF, Swiss franc; NA, not applicable; CEA, cost-effectiveness analysis.

ClinicoEconomics and Outcomes Research 2014:6

submit your manuscript | www.dovepress.com 323

Dovepress
In all studies comparing different ESA regimens, the targeted Hb value, as well as the baseline and endpoint values for Hb and iron status (ie, transferrin saturation and ferritin), are critical. The available data for Hb levels are outlined in Table 4. The Hb targets were significantly varied in the studies demonstrating higher costs after switching to CERA, and these targets were not defined in the majority of studies demonstrating definite cost reduction. Furthermore, a lack of standardization of iron parameters was obvious (data not shown).

A literature search of the conference abstract databases revealed four other studies that predicted the probability of cost savings after the introduction of CERA, or following the switch from a regimen with short-acting EPO to CERA (Table 5).\(^\text{42–45}\) All these data were presented at European International Society for Pharmacoeconomics and Outcomes Research conferences, but they are still not available as regular articles in peer-reviewed journals. These studies include two CEAs that presented decision trees simulating treatment costs for the Mexican and Ukrainian public health care systems, respectively, and one CMA from Poland.\(^\text{42–44}\) Gonzalez et al\(^\text{42}\) estimated a slight reduction of treatment costs after switching to CERA from EPO alpha, with probabilities of 0.60 for cost savings and 0.99 for cost efficiency. Moreover, the hospital stay of treated patients due to Hb variations was reduced by 37%.\(^\text{42}\) For the Ukrainian dialysis population, estimated cost savings were 5%–35%, depending on the route of administration.\(^\text{43}\) Kawalec et al\(^\text{44}\) performed a CMA from the perspective of the public payer for predialysis patients and found a cost savings of €262.4/patient over a 2-year horizon compared to treatment with DA. Finally, assuming that CERA achieves a market share of 40%, Walsh et al\(^\text{45}\) calculated a possible ESA budget reduction by 15% in five EU countries based on a United Kingdom budget impact model.

Three observational multicenter time and motion (TAM) studies predicted an average annual time savings of >80% assuming 100% CERA use for the treatment of anemia in dialysis patients (Table 6).\(^\text{46–48}\) Of note, a significant overlap in the available data cannot be excluded, as results presented by Klatko and Felisiak\(^\text{46}\) from three Polish HD centers seem to be included in a study from De Cock et al,\(^\text{47}\) who incorporated a total of 20 centers from five EU countries. In both studies, time (but not direct costs) was investigated.

Saueressig et al\(^\text{46}\) calculated that with the adoption of once-monthly CERA, health care staff members’ time for “observed” activities (including the preparation, distribution, injection, and ordering of ESAs) alone could be reduced by 70%–84%, saving 24–35 working days per year for a center of 100 patients. When nonobserved activities are considered as well, once-monthly CERA could offer potential annual time savings of 43 days in an average German center, and 37 days in an average UK center. Translated into monetary units, this could lead to an estimated reduction in annual costs of 58% for the German center and 35% for the UK center. Similar time saving ratings were confirmed by De Cock et al,\(^\text{47}\) prognosticating a 67%–95% time reduction, depending on center size and the initial distribution of conventional ESAs. In addition, a comparison between DA and CERA indicated that there was still a substantial reduction in estimated annual time savings, ranging between 40% in France and 58% in Italy.\(^\text{47}\)

### Table 4 Reported hemoglobin levels in studies analyzing the cost-effectiveness of CERA

| Study | Hb target (g/dL) | Mean Hb during the study (g/dL) |
|-------|-----------------|-------------------------------|
| Studies demonstrating increased medication costs after switching to CERA | | |
| Silva et al\(^\text{41}\) | ND | NA |
| Escudero-Vilaplana et al\(^\text{42}\) | ND | NA |
| Albero Molina et al\(^\text{43}\) | 11.0–13.0 | BL (11.6±0.6) versus month 6 (11.5±0.9) |
| Tsai et al\(^\text{44}\) | 9.0–12.0 | BL (10.2±0.7) versus month 6 (10.1±1.4) |
| Padullés-Zamora et al\(^\text{45}\) | 10.0–12.0 | BL (10.6/11.4) versus month 12 (11.3/11.4) |
| Olmos et al\(^\text{46}\) | ND | Average: 9.8–11.0 |
| Studies demonstrating definite cost reduction after switching to CERA | | |
| Müller and Molli\(^\text{47}\) | ND | BL (10.9±1.2) versus month 7 (10.9±1.3) |
| Franz et al\(^\text{48}\) | ND | BL (11.7) versus month 6 (11.6) |
| Cynke et al\(^\text{49}\) | ND | BL (11.8) versus month 15 (11.3) |
| Franz and Cynke\(^\text{50}\) | ND | BL (11.8) versus month 5 (11.8) |
| Echarri Arrieta et al\(^\text{51}\) | 11.0–12.0 | DA: 30.4% reached target CERA: 65% reached target |

**Notes:** ESA naïve patients; †patients that were pretreated with ESA.

**Abbreviations:** CERA, continuous erythropoietin receptor activator; Hb, hemoglobin; ND, not determined; NA, not assessed; BL, baseline; DA, darbepoetin alpha.
importance for both payers and clinicians. The administration of CERA once a month could have an advantage of cost and time reduction. Thus, the currently published literature focusing on the cost-effectiveness of CERA in anemia treatment was critically analyzed.

From the clinician’s point of view, although multiple studies have supposedly demonstrated the clinical safety and efficacy of CERA, peer-reviewed literature analyzing the definite cost-effectiveness of CERA is scarce. Most of the available data originate from conference abstracts and are

Table 5 Studies predicting cost reduction with CERA treatment

| Study                  | Design and setting                          | Patient number, type, age (years) | Duration (months) | Comparator ESAs and median doses | Costs                                                                 |
|------------------------|---------------------------------------------|----------------------------------|-------------------|---------------------------------|----------------------------------------------------------------------|
| Gonzalez et al13 (MA)  | CEA, on base of decision tree; Mexico       | NA                               | NA                | Epo alpha                       | Reduction of treatment costs/year: 4.53%. Average costs/patient/year: Epo alpha (US $2.907 [–$2.106]) versus CERA (US $2.776 [–$2.011]) |
| Bezditko et al13 (MA)  | CEA, on base of decision tree; Ukraine       | 3,400; D; NA                     | NA                | Epo alpha, Epo beta, DA         | Estimated cost savings: 5%–35% Average costs/patient/month: Short-acting Epo IV (US $184–$267 [–$141–$205]) versus CERA IV (US $173 [–$133]) |
| Kawalec et al14 (MA)   | CMA, sensitivity analysis, public payer perspective; Poland | NA; pre-D; NA                   | 24                | DA (10 μg/week) SC, CERA (50 μg/month) | Reduction of treatment costs/patient in 2 years with CERA PLN 1.194 (–€262) Results confirmed by sensitivity analysis After 5 years, increase in CERA use to 40% Reduces ESA budget by 15% |
| Walsh et al15 (MA)     | Retrospective, multicenter, UK budget impact model; five EU countries (UK, Italy, Germany, Spain, France) | 2,029; pre-D, HD; NA            | 12                | Epo alpha (pre-D: 19.350 IU/month; HD: 35,404 IU/month), Epo beta (pre-D: 18.230 IU/month; HD: 36,789 IU/month), DA (pre-D: 107 μg/month; HD: 169 μg/month), CERA (pre-D: 98 μg/month; HD: 150 μg/month) | Estimated cost savings: €9.798 (–58%) for German HD center and GBP 6,615 (–35%) for UK center Assuming 100% CERA use once monthly: 79% Germany, 84% UK Estimated cost savings: €9.798 (–58%) for German HD center and GBP 6,615 (–35%) for UK center Assuming 100% CERA use once monthly: 76%–89% (depending on center size and ESA distribution) For switch from DA to CERA, still a substantial time savings (40%–58%) Cost was not investigated Assuming 100% CERA use once monthly: 82%–88% Cost was not investigated |

Note: In order to enhance the comparability between different studies, all currencies were translated into Euros (€).

Abbreviations: CERA, continuous erythropoietin receptor activator; ESA, erythropoiesis stimulating agent; MA, meeting abstract; CEA, cost-effectiveness-analysis; NA, not available; Epo, epoetin; Hb, hemoglobin; Hct, hematocrit; D, dialysis; DA, darbepoetin alpha; iv, intravenous; SC, subcutaneous; CMA, cost-minimization analysis; PLN, Polish Zloty; EU, European Union; HD, hemodialysis.

Table 6 Studies predicting a significant gain in time with CERA treatment in dialysis centers

| Study                  | Design and setting                          | Patient number, type, age (years) | Duration (months) | Comparator ESAs | Estimated annual time and cost savings |
|------------------------|---------------------------------------------|----------------------------------|-------------------|-----------------|--------------------------------------|
| Saueressig et al16 (PRJ) | Prospective, TAM method, multicenter, 12 HD centers; Germany, UK | 1,200; hypothetical              | NA                | Epo alpha, Epo beta, DA, CERA   | Assuming 100% CERA use once monthly: 79% Germany, 84% UK Estimated cost savings: €9.798 (–58%) for German HD center and GBP 6,615 (–35%) for UK center |
| De Cock et al17 (PRJ)  | Observational TAM study, multicenter, 20 HD centers (hospital-based or ambulatory); France, Germany, Italy, Poland, Spain | NA                              | NA                | Epo alpha, Epo beta, DA, CERA   | Assuming 100% CERA use once monthly: 76%–89% (depending on center size and ESA distribution) For switch from DA to CERA, still a substantial time savings (40%–58%) Cost was not investigated |
| Klatko and Felisiak18 (PRJ) | Prospective, TAM study, multicenter, three HD centers; Poland | NA                              | NA                | Epo alpha, Epo beta, CERA       | Assuming 100% CERA use once monthly: 82%–88% Cost was not investigated |

Abbreviations: CERA, continuous erythropoietin receptor activator; ESA, erythropoiesis; PRJ, peer-reviewed journal; TAM, time and motion; NA, not assessed; Epo, epoetin; DA, darbepoetin alpha; HD, hemodialysis; GBP, Great British pounds.
therefore surrounded by a considerable degree of uncertainty and are open to biases of unknown magnitude and direction. Possible caveats in the interpretation of the reviewed literature are summarized in Table 7. In addition, it is noteworthy that the reviewed literature was analyzed and interpreted by a clinician and not a pharmacoecnomist.

The identified literature was completely restricted to the treatment of anemia due to CKD. Although the majority of studies suggested a considerable cost advantage for CERA, the published literature cannot easily be compared. While TAM studies clearly indicate that a switch to CERA could minimize ESA treatment time and its subsequent costs, the results of studies comparing direct medication costs are more ambivalent, potentially reflecting significant differences between health care systems and centers. In addition, the selected literature presents a mix of cost estimates in European and non-European currencies, and despite attempts to translate the currency into Euros, the comparability between different currencies and different public health systems is not possible. In general, whether the studies have relied on published prices rather than actual market prices remains unclear.

For the switch from short-acting to long-acting ESAs, a conversion guideline is mandatory. Most clinicians act in accordance with the dose conversion referral provided by the manufacturer to reduce potentially harmful Hb variability. Due to the deficiency in the available data, it remains unclear whether applied dose conversion ratios were comparable between the cited studies.

Furthermore, the CERA doses required to maintain stable Hb values over longer treatment periods seem to vary significantly in different anemic cohorts. For example, in stable HD patients, a couple of studies have suggested decreasing CERA doses over time, whereas others argue for increasing dosages. A study conducted with 52 Japanese HD patients showed that CERA doses decreased during a 28-week study. In contrast, the randomized comparative PATRONUS (comParator sTudy of CERA and darbepOetin alfa in patieNts Undergoing dialySis) trial conducted with 490 HD patients demonstrated a dose increase of 6.8% after switching from once-weekly DA to once-monthly CERA.

For unstable or critically ill patients in particular, estimations of the CERA dose requirements and their associated costs are currently unpredictable. Albero Molina et al reported a further increase in the average costs associated with CERA in HD patients at month 6. This is potentially due to the fact that treated patients were more critically ill, as reflected by a distinct drop-out rate during follow-up. Of the 30 patients who began the study, 13 were withdrawn during the 6-month study because of “death, transplantation or a process that might interfere with the Hb level.”

Time savings that can be converted into cost reductions is an important reason for a clinician to switch to a long-acting ESA with reduced dosing frequency. However, it is still unclear whether there really is a cost advantage for switching between two long-acting ESAs. Outside of interventional clinical studies, only limited information is published on switching ESA treatment from DA to CERA in renal anemia. In the AFFIRM (Aranesp® Efficiency Relative to Mircera®) study, HD patients were switched from DA to CERA. The number of RBC transfusions increased approximately threefold from the preswitch to the postswitch period. In addition, compared to DA, the authors discovered a lower Hb response to CERA and inferior iron utilization, as estimated by hepcidin levels, using dosages recommended by the company. Unfortunately, health care resource utilization and cost data were not collected in this study, preventing a comparison of these variables between the preswitch and postswitch periods.

Of note, the current literature query found cost-effectiveness after switching from DA to CERA in the majority of the studies analyzed. A total of six studies reported cost savings, another study by De Cock demonstrated substantial time savings, whereas only two authors reported slightly higher costs for CERA compared to DA (median costs/patient/month of €147.5 and €105±€26 versus €134.4 and €115±€17, respectively). However, it remains unclear whether general conclusions can be drawn from these observations, as many patients may

Table 7 Caveats for the interpretation of studies assessing the cost-effectiveness of CERA

| Paucity of published data | Quality of published data unknown (results predominantly from meeting abstracts) |
| Differences and variability between public health systems, countries, and centers | Real-life studies (for example, real costs versus theoretical costs; published prices versus actual market prices) |
| Dose conversion ratios often not comparable | Comparability of targeted Hb values and iron parameters? |
| RBC transfusions preswitch and postswitch? | Iron, vitamin B12, and folate supplementation during study period? |

**Methodology**

- CEA: are minimal requirements fulfilled?
- CMA: significance?
- TAM studies: can time savings easily be converted into cost savings and monetary units?

**Abbreviations:** CERA, continuous erythropoietin receptor activator; Hb, hemoglobin; RBC, red blood cell; CEA, cost-effectiveness analysis; CMA, cost-minimization analysis; TAM, time and motion.
also be successfully managed with a once-monthly dose of DA.55,56

Recent randomized trials comparing target Hb levels >13 g/dL with target levels of 10–12 g/dL resulted in serious concerns about the safety of ESA therapy in CKD patients not on dialysis.10–13 Consequently, the US FDA now recommends using the lowest possible ESA doses with gradual increases in order to avoid the need for transfusions, but without exceeding Hb concentrations of 12 g/dL.57 Although Hb targets were predominantly not defined,31,32,36,37–40 or given that they showed a distinct variation in the analyzed studies (see Table 4),33–35,41 the average baseline and endpoint Hb values reached above the proposed levels of 10–12 g/dL. A detailed declaration regarding the number of RBC transfusions administered in the preswitch and postswitch periods, as well as specifications regarding vitamin B12 or folate supplementation, are missing.

Functional iron deficiency with low circulating iron and normal or increased storage iron translated into low transferrin saturation; moreover, normal or high serum ferritin is commonly seen in CKD patients.58,59 Inadequate iron availability limits the response to ESA.6 Unfortunately, all studies summarized in this review do not include a detailed description of iron administration. This lack of standardization poses a challenge and can lead to confusion when comparing these data. Although there are some promising data for CERA regarding its improvement of iron utilization, further studies have to prove if maximal cost-effectiveness after CERA switch can only be reached with optimal iron substitution.32,60,61

In a health economic evaluation analysis of different health care interventions, a variety of methods can be applied by the investigators.62 These methods to assess costs and effects between (for example) two or more ESA comparators should include a cost–benefit analysis, a cost–utility analysis, CEA, or CMA.63–66 Only six of the 18 selected studies in this review established a CEA or CMA to evaluate the cost-effectiveness of CERA.31,32,41–44 Moreover, for all of the studies that applied CEA or CMA, access was limited to abstracts and not to full-text articles. Therefore, it is currently not possible to estimate if all obligatory requirements for CEA concordant with published consensus guidelines were fulfilled in these studies. For example, it has been recommended that CEA be conducted from a societal perspective, and that a lifetime horizon be employed, since only these approaches avoid allocation biases that may be introduced by a narrower approach.67–69 In addition, it is not possible to compare the different CEA, as no universal outcomes were indicated. Finally, some experts in this field believe that CMA is an appropriate method of analysis, but only under rare circumstances.70,71 Taken together, due to methodological ambiguity, conclusions from the reported CEAs and CMAs cannot be easily derived.

TAM studies are defined in the National Library of Medicine’s controlled vocabulary thesaurus as “the observation and analysis of movements in a task with emphasis on the amount of time required to perform the task”.72 TAM studies have proven to be the gold standard method to measure and quantify clinical workflow.73

The collection of observational data for ESA treatment-related activities should allow for a realistic estimation of the average times spent on each activity. Tasks suitable for the TAM studies were the activities related to the preparation, distribution, injection, recordkeeping, and ordering of ESAs.46–48 Of particular note, the respective portion of these activities shows a significant variation in different clinical settings. For example, in ambulatory dialysis units, frequent ESA dosing places a substantial burden on nursing time, whereas self-administration of long-acting ESAs at home is often routine for peritoneal dialysis patients.30,42

In parallel to the landmark study conducted by Schiller et al.30 all three TAM studies included in this review estimated that 100% conversion to once-monthly CERA would reduce nursing ESA administration time by approximately 80% in dialysis units. While costs were not investigated in the reports by De Cock et al.77 and Klato and Felisiak,78 respectively, Saueressig et al.76 estimated a resultant cost savings of between 35%–58%.

Here, an important question arises: can time be easily translated into monetary units? All three TAM studies were multicenter-based, which can be a strength but also a weakness.46–48 From the current author’s point of view, these data should be interpreted with caution, as well known limitations of TAM studies are their extreme variability in time for prespecified tasks, and in the results observed between different centers and treatment settings (for example, public hospital versus private practice settings), making the pooling of data with the equal weighting of each center difficult. The inclusion of different regional locations, and even different EU countries with entirely different health care systems, further complicates generalization of these results.

Financial reasons were the driving force behind the development of biosimilar erythropoietins that were introduced after patents of short-acting ESAs had expired.79 EPO biosimilars approved by the European Medicines Agency or the US FDA have been shown to have a comparable efficacy
and safety profile to their originators. Unfortunately, studies comparing the costs between CERA and biosimilar erythropoietins are still absent in the literature.

Effective long-acting competitors on the ESA market are DA and CERA, with Amgen’s DA acting as a “monopolist” on the US market. In this context, a marketing survey assessed nephrologists’ interest in and anticipation of the expected 2014 arrival of CERA on the US market. Half of the surveyed nephrologists believed that approximately 40% of their CKD patients are potential CERA candidates, suggesting that CERA could have a significant impact on the US renal anemia market in the coming years. Despite these survey results, the fate of CERA on the highly competitive US market is currently unpredictable.

**Conclusion**

As safety concerns for CERA are still limited, and recent studies have demonstrated similar efficiency compared to DA and conventional short-acting ESAs, the cost-effectiveness of CERA could become the pivotal reason for clinicians to prescribe this remedy. Unfortunately, the current literature provides only little evidence to support such a decision. Therefore, well-designed, head-to-head studies with defined endpoints directly comparing costs in similar patient populations treated with equipotent CERA and comparator doses are now urgently needed.

**Acknowledgment**

The author thanks Dr Nicole Bick from Roche Pharma AG Grenzach-Wyhlen for helpful assistance in the literature search.

**Disclosure**

The author reports no conflicts of interest in this work.

**References**

1. Culleton BF, Manns BJ, Zhang J, Tonelli M, Klarenbach S, Hemmelgarn BR. Impact of anemia on hospitalization and mortality in older adults. *Blood*. 2006;107(10):3841–3846.
2. Weiss G, Goodnough LT. Anemia of chronic disease. *N Engl J Med*. 2005;352(10):1011–1023.
3. Goodnough LT, Schrier SL. Evaluation and management of anemia in the elderly. *Am J Hematol*. 2014;89(1):88–96.
4. Murphy MF, Wallington TB, Kelsey P, et al; British Committee for Standards in Haematology, Blood Transfusion Task Force. Guidelines for the clinical use of red cell transfusions. *Br J Haematol*. 2001;113(1):24–31.
5. Eschbach JW, Abdulhai MH, Browne JK, et al. Recombinant human erythropoietin in anemic patients with end-stage renal disease. Results of a phase III multicenter clinical trial. *Ann Intern Med*. 1989;111(12):992–1000.
6. KDIGO clinical practice guidelines for anemia in chronic kidney disease. *Kidney Int Suppl*. 2012;2(4):288–291.
7. Rizzo JD, Brouwers M, Hurley P, et al; American Society of Hematology and the American Society of Clinical Oncology Practice Guidelines Update Committee. American Society of Hematology/American Society of Clinical Oncology clinical practice guideline update on the use of epoetin and darbepoetin in adult patients with cancer. *Blood*. 2010;116(20):4045–4059.
8. rote-liste.de [homepage on the Internet]. Frankfurt, Germany: Rote Liste® Service GmbH [updated 2014; cited January 23, 2014]. Available from: http://rote-liste.de/. Accessed June 13, 2014.
9. Collins AJ, Foley RN, Herzog C, et al. Excerpts from the US Renal Data System 2009 Annual Data Report. *Am J Kidney Dis*. 2010;55(1 Suppl 1):S1–S420, A6.
10. Besarab A, Bolton WK, Browne JK, et al. The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. *N Engl J Med*. 1998;339(9):584–590.
11. Singh AK, Szczepch L, Tang KL, et al; CHOIR Investigators. Correction of anemia with epoetin alfa in chronic kidney disease. *N Engl J Med*. 2006;355(20):2085–2098.
12. Driéke TB, Locatelli F, Clyne N, et al; CREATE Investigators. Normalization of hemoglobin level in patients with chronic kidney disease and anemia. *N Engl J Med*. 2006;355(20):2071–2084.
13. Pfeiffer MA, Burdman EA, Chen CY, et al; TREAT Investigators. A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. *N Engl J Med*. 2009;361(21):2019–2032.
14. Curran MP, McCormack PL. Methoxy polyethylene glycol-epoetin beta: a review of its use in the management of anaemia associated with chronic kidney disease. *Drugs*. 2008;68(8):1139–1156.
15. Panchapakesan U, Samual S, Pollock C. Nanomedicines in the treatment of anemia in renal disease: focus on CERA (Continuous Erythropoietin Receptor Activator). *Int J Nanomedicine*. 2007;2(1):33–38.
16. Levin NW, Fishbane S, Cañedo FV, et al; MAXIMA study investigators. Intravenous methoxy polyethylene glycol-epoetin beta for haemoglobin control in patients with chronic kidney disease who are on dialysis: a randomised non-inferiority trial (MAXIMA). *Lancet*. 2007;370(9596):1415–1421.
17. Macdougall IC, Walker R, Provenzano R, et al; ARCTOS Study Investigators. CERA corrects anemia in patients with chronic kidney disease not on dialysis: results of a randomized clinical trial. *Clin J Am Soc Nephrol*. 2008;3(2):337–347.
18. Locatelli F, Mann JF, Aldigier JC, et al; CERA safety profile: a pooled analysis in patients with chronic kidney disease. *Clin Nephrol*. 2010;73(2):94–103.
19. Dellanna F, Winkler RE, Bozkurt F, et al; MIRACEL Study Group. Dosing strategies for conversion of haemodialysis patients from short-acting erythropoiesis stimulating agents to once-monthly CERA: experience from the MIRACEL study. *Int J Clin Pract*. 2011;65(1):64–72.
20. Gascon P, Pirker R, Del Mastro L, Durrwell L. Effects of CERA (continuous erythropoietin receptor activator) in patients with advanced non-small-cell lung cancer (NSCLC) receiving chemotherapy: results of a phase II study. *Ann Oncol*. 2010;21(10):2029–2039.
21. Schmidt RJ. Methoxy polyethylene glycol-epoetin beta: worth waiting for or a novelty worn off? *Expert Opin Pharmacother*. 2009;10(9):1509–1514.
22. Patent docs Biotech & Pharma Patent Law & News Blog [webpage on the Internet]. Available from: http://www.patentdocs.org/2009/12/ammen-and-hoffmanlaroche-settle-mircera-litigation.html. Accessed June 8, 2014.
23. Meguid El Nahas A, Bello AK. Chronic kidney disease: the global challenge. *Lancet*. 2005;365(9456):331–340.
24. Bray F, Jemal A, Grey N, Ferlay J, Forman D. Global cancer transitions according to the Human Development Index (2008–2030): a population-based study. *Lancet Oncol*. 2012;13(8):790–801.
25. Duh MS, Weiner JR, White LA, Lefebvre P, Greenberg PE. Management of anaemia: a critical and systematic review of the cost-effectiveness of erythropoiesis-stimulating agents. *Pharmacoeconomics*. 2008;26(2):99–120.
26. Becker R, Dembek C, White LA, Garrison LP. The cost offsets and cost-effectiveness associated with pegylated drugs: a review of the literature. Expert Rev Pharmacoecon Outcomes Res. 2012;12(6):775–793.

27. Burnier M, Douchamps JA, Tanghe A, et al. Less frequent dosing of erythropoiesis stimulating agents in patients undergoing dialysis: a European multicentre cost study. J Med Econ. 2009;12(2):77–86.

28. Churchill DN, Macarios D, Attard C, Kallich J, Goeree R. Costs associated with erythropoiesis-stimulating agent administration to hemodialysis patients. Nephron Clin Pract. 2007;104(4):c193–c198.

29. Bernardo M, Crawford P, Hertel J, et al. Assessment of time and practice resources required to provide weekly or monthly erythropoiesis-stimulating protein therapy to chronic kidney disease patients in the physician office setting. J Manag Care Pharm. 2006;12(9):714–725.

30. Schiller B, Doss S, DE Cock E, Del Aguila MA, Nissenson AR. Costs of managing anemia with erythropoiesis-stimulating agents during hemodialysis: a time and motion study. Hemodial Int. 2008;12(4):441–449.

31. Silva FHCV, Vianna CMDM, Silva FVC. PUK3 Cost-effectiveness of Anemia Treatment in Dialysis Patients in Brazil: ISIS 3rd Latin America Conference, Mexico City, Mexico, 8–10 September 2011. Value in Health. 2011;14(7):A570.

32. Escudero-Vilaplana V, Martínez-Nieto C, López-Gómez JM, Vega-Martínez A, Bellón-Canó JM, Sanjurjo-Sáez M. Erythropoiesis-stimulating agents in anemia due to chronic kidney disease: a cost-minimization analysis. Int J Clin Pharm. 2013;35(3):463–468.

33. Albero Molina MD, López-Menacho Martínez R, del Pozo Fernández C, Álvarez Fernández L, Sánchez Rodríguez L. Efficiency of monthly subcutaneous administration of methoxy-polyethylene glycol-epoetin beta (Mircera) in stable patients under hemodialysis previously treated with erythropoietin. Dialysis & Transplantation. 2013;34(3):93–100. Spanish.

34. Tsai MH, Yang WY, Leu JG. Shifting darboepoetin alpha to subcutaneous methoxy polyethylene glycol-epoetin beta of similar doses and extended dose intervals effectively maintains hemoglobin concentrations in peritoneal dialysis patients. Acta Nephrologica. 2013;27(2):99–103.

35. Padulles-Zamora N, Comas-Salgueiras D, Pineda-Yuste Mdel J, Jódar-Masané R, Martínez-Castellano A. Use of methoxy polyethylene glycol-epoetin beta in stage 3, 4 or 5 non-dialysis chronic kidney disease. Nefrologia. 2012;32(2):221–227.

36. Olmos V, Pignataro J, Olmos I, Daners M. Assessment of Compliance to the Treatment of Anaemia in Patients Receiving a Novel ESA – Methoxy Polyethylene Glycol-Epoetin Beta (MIRCERA®) – Versus Conventional Erythropoietin. Available from: http://www.tshp.tmall.net/attachments/106_V1714-%E5%B0%88%E9%A1%8C.pdf. Accessed January 12, 2014.

37. Müller A, Moll M. Switching hemodialysis patients from short-acting ESA to once monthly CERA: A single center experience. World Congress of Nephrology; April 8–12, 2011; Vancouver, British Columbia. Abstract SU484.

38. Franz S, Jäger C, Gauthier T. Hemoglobin levels and development of ESA dose in hemodialysis patients after conversion to CERA A multi-center observational study. In: Swiss Medical Weekly; 2009;139(45/46 Suppl 178): Abstract 85 4.4. Annual Meeting of the Swiss Society of Nephrology; December 2–4, 2009; Interlaken, Switzerland.

39. Cykne E, Benz B, Franz S. Stable hemoglobin values and lower dose requirements after complete conversion from epoetin beta to CERA A single center experience. In: Swiss Medical Weekly; 2009;139(45/46 Suppl 178): Abstract 195 53. Annual Meeting of the Swiss Society of Nephrology; December 2–4; 2009; Interlaken, Switzerland.

40. Franz S, Cykne E. Development of dose and costs after conversion to CERA in hemodialysis patients. In: Swiss Medical Weekly; 2008;138(47/48 Suppl 167): Abstract 235 69. 40th Annual Meeting of the Swiss Society of Nephrology; December 3–5; 2008; St Gallen, Switzerland.

41. Echarri Arrieta E, Fernandez Ferreiro F, Alonso Valente A, Martinez Gutin M, Martinez Calvo M. Cost-effectiveness analysis of patients in peritoneal dialysis with methoxy polyethylene glycol-epoetin beta versus darboepoetin alfa in Santiago de Compostela University hospital complex, Spain. Poster presented at: OHP020, 17th Congress of the European Association of Hospital Pharmacists; March 21–23; 2012; Milan, Italy.
60. Kakimoto-Shino M, Toya Y, Kuji T, Fujikawa T, Umemura S. Changes in hepcidin and reticulocyte hemoglobin equivalent levels in response to continuous erythropoietin receptor activator administration in hemodialysis patients: a randomized study. Ther Apher Dial. Epub January 24, 2014.

61. Hashimoto T, Tsugawa Y, Tsunoda M, Ikee R, Sasaki N, Hashimoto N. Importance of intensive iron supplementation for dialysis patients with continuous erythropoietin receptor activator. J Am Soc Nephrol. 2012;23:769A–770A Abstract SA-PO570. ASN Kidney Week, October 30–November 4, 2012; San Diego, CA, USA.

62. Chang WY, Henry BM. Methodologic principles of cost analyses in the nursing, medical, and health services literature, 1990–1996. Nurs Res. 1999;48(2):94–104.

63. Russell LB, Gold MR, Siegel JE, Daniels N, Weinstein MC. The role of cost-effectiveness analysis in health and medicine. Panel on Cost-Effectiveness in Health and Medicine. JAMA. 1996;276(14):1172–1177.

64. Weinstein MC, Siegel JE, Gold MR, Kamlet MS, Russell LB. Recommendations of the Panel on Cost-effectiveness in Health and Medicine. JAMA. 1996;276(15):1253–1258.

65. Siegel JE, Weinstein MC, Russell LB, Gold MR. Recommendations for reporting cost-effectiveness analyses. Panel on Cost-Effectiveness in Health and Medicine. JAMA. 1996;276(16):1339–1341.

66. Udvarhelyi IS, Colditz GA, Rai A, Epstein AM. Cost-effectiveness and cost-benefit analyses in the medical literature. Are the methods being used correctly? Ann Intern Med. 1992;116(3):238–244.

67. Drummond MF, Sculpher MJ, Torrance G, O’Brien B, Stoddart G. Methods for the Economic Evaluation of Health Care Programmes. 2nd ed. Oxford, UK: Oxford University Press; 1997.

68. Robinson R. Cost-effectiveness analysis. BMJ. 1993;307(6907):793–795.

69. Lefebvre P, Vekeman F, Cremieux PY. Comment: the impact of methodological approach on cost findings in comparison of epoetin alfa with darbepoetin alfa. Ann Pharmacother. 2010;44(3):595; author reply 595–596.

70. Briggs AH, O’Brien BJ. The death of cost-minimization analysis? Health Econ. 2001;10(2):179–184.

71. Robinson R. Costs and cost-minimisation analysis. BMJ. 1993;307(6906):726–728.

72. National Institutes of Health [webpage on the Internet]. Fact sheet: Medical Subject Headings (MeSH®). Bethesda, MD: U.S. National Library of Medicine; 2013. Available from: https://www.nlm.nih.gov/pubs/factsheets/mesh.html. Accessed January 24, 2014.

73. Lopetegui M, Yen PY, Lai AM, Embi PJ, Payne PR. Time Capture Tool (TimeCaT): development of a comprehensive application to support data capture for Time Motion Studies. AMIA Annu Symp Proc. 2012;2012:596–605.

74. Jelkmann W. Biosimilar recombinant human erythropoietins (“epoetins”) and future erythropoiesis-stimulating treatments. Expert Opin Biol Ther. 2012;12(5):581–592.

75. Hörl WH. Differentiating factors between erythropoiesis-stimulating agents: an update for selection for anaemia of chronic kidney disease. Drugs. 2013;73(2):117–130.

76. BioTrends Research Group [webpage on the Internet]. Should Mircera reach the U.S. market, surveyed nephrologists state that at least 40 percent of CKD-ND and dialysis patients are likely candidates. Exton, PA: BioTrends Research Group; 2013. Available from: http://www.biotrends.com/News-and-Events/Press-Releases/Mircera-Nephrolodists-State-Candidates-100113. Accessed January 31, 2014.