

ORIGINAL RESEARCH

# Less frequent dosing of erythropoiesis stimulating agents in patients undergoing dialysis: a European multicentre cost study

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## Abstract

**Objective:** To calculate the variable costs involved with the process of delivering erythropoiesis stimulating agents (ESA) in European dialysis practices.

**Methods:** A conceptual model was developed to classify the processes and sub-processes followed in the pharmacy (ordering from supplier, receiving/storing/delivering ESA to the dialysis unit), dialysis unit (dose determination, ordering, receipt, registration, storage, administration, registration) and waste disposal unit. Time and material costs were recorded. Labour costs were derived from actual local wages while material costs came from the facilities' accounting records. Activities associated with ESA administration were listed and each activity evaluated to determine if dosing frequency affected the amount of resources required.

**Results:** A total of 21 centres in 8 European countries supplied data for 142 patients (mean) per hospital (range 42–648). Patients received various ESA regimens (thrice-weekly, twice-weekly, once-weekly, once every 2 weeks and once-monthly). Administering ESA every 2 weeks, the mean costs per patient per year for each process and the estimates of the percentage reduction in costs obtainable, respectively, were: pharmacy labour (€10.1, 39%); dialysis unit labour (€66.0, 65%); dialysis unit materials (€4.11, 61%) and waste unit materials (€0.43, 49%).

**Limitation:** Impact on financial costs was not measured.

**Conclusion:** ESA administration has quantifiable labour and material costs which are affected by dosing frequency.

**Key words:** administration; cost savings; erythropoiesis stimulating agents; Europe; haemodialysis

## Introduction

Erythropoiesis stimulating agents (ESAs) have markedly improved the management of anaemia secondary to chronic kidney disease (CKD) as well as the quality of life of patients. A key factor affecting the indirect costs of anaemia management with ESAs is the dosing schedule. Darbepoetin alfa is administered either weekly (QW) or every 2 weeks (Q2W) for patients undergoing haemodialysis<sup>1,2</sup>. Two European studies have demonstrated improved operational efficiency by extending the dosing intervals in patients with CKD by switching patients from epoetin alpha to darbepoetin alfa treatment<sup>3,4</sup>. The benefits of less frequent dosing are not just limited to healthcare personnel. In a study

of patients with CKD not on dialysis, patients and their families were also positively affected with respect to routine anaemia management when ESAs were administered at extended intervals in the physician's office<sup>5</sup>.

Due to budget constraints, the cost of any treatment is coming under scrutiny by healthcare providers all over the world and ESA treatment is no exception. Canadian estimates of the non-acquisition costs of subcutaneous ESA therapy in a haemodialysis unit have shown a substantial annual cost burden to healthcare providers, and have underlined the importance of activity-based costing that accounts for the time taken preparing and administering the drug and for monitoring therapy<sup>6</sup>.

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30 To investigate the situation further, this study was  
 conducted to calculate the costs involved with the entire  
 process of ESA delivery in Europe, from the initial drug  
 order placement to the incineration of the ESA syringe.  
 We wanted to find out whether cost savings would be  
 35 possible with Q2W dosing. Here we present the results of  
 the first study conducted in eight European countries  
 that describes the whole process of ESA delivery at each  
 study centre. We believe that the results of this study may  
 help establish a benchmark for sharing best practice  
 40 among European haemodialysis centres.

## Methods

### 45 *Study design*

The study was designed to measure all possible  
 quantitative and qualitative advantages for the hospital  
 or the haemodialysis centre associated with reducing  
 the frequency of administering ESA. The quantitative  
 50 aspect of the study included the time and material cost  
 savings of the processes related to the administration of  
 ESA in four departments: the pharmacy, dialysis unit,  
 waste unit and back-office (Figure 1). The qualitative advan-  
 55 tages included the organisational efficiency advantages,  
 logistic efficiency advantages and process improvement.

The determination of the advantages of Q2W dosing  
 was estimated for two dosing scenarios: firstly, the  
 current ESA dosing situation and then switch to darbe-  
 60 poetin alfa administered Q2W, and secondly, epoetin  
 administered thrice-weekly (TIW) and then switch to  
 darbepoetin alfa Q2W. For the epoetin to darbe-  
 poetin alfa conversion, the recommendation stated in  
 the Aranesp\* Summary of Product Characteristics of  
 200:1 was applied.

### 65 *Data collection*

68 Data were collected via interviews with relevant  
 69 stakeholders of haemodialysis, observations at the four  
 70 departments, and time measurements of the activities  
 (Figure 2). From the information gathered from the  
 interviews and observations, a generic process model was  
 developed to classify the processes and sub-processes  
 75 routinely followed in the pharmacy (ordering from  
 supplier, receiving and storing and delivering ESA to the  
 dialysis unit) and in the dialysis unit (dose determina-  
 tion, ordering procedures, receipt and storage of ESAs  
 and ESA administration). The generic process flow was  
 80 used to develop the hospital specific process flow. Based  
 on interviews and observations, we were able to identify

which activities are influenced by a change in the  
 frequency of administering ESA treatment. 85

### *Input data*

For the processes and activities affected by less frequent  
 90 ESA dosing, time measurements were made that,  
 together with the other data collected for material costs,  
 formed the input for the calculation of the time and  
 material savings. Time measurements were made with a  
 stopwatch by independent researchers and several  
 95 measurements were taken at random for each individual  
 involved in a process. Every single step (e.g., taking  
 syringe - opening package - taking out disinfect  
 ion tissue - opening package and so on) in a process  
 (e.g., administer ESA) was observed and measured. The  
 100 average time was calculated for every step measured.

The order data, distribution data and administration  
 data were collected at the research site and were  
 combined with the hospital specific data (wages, prices  
 of materials needed at dialysis unit). Order data included  
 105 all ESA orders (darbepoetin alfa, epoetin alpha, epoetin  
 beta) from the pharmacy or purchasing department to the  
 suppliers over a period of 1 year and for all dosages used.  
 The distribution data included ESA deliveries from the  
 pharmacy to the dialysis unit (as well as all ESA orders  
 110 from the dialysis unit to the pharmacy) over a period of  
 1 year and all dosages used at the dialysis unit. Data on  
 ESA administration were collected for 16 weeks, and the  
 analyses were based on the last 4 weeks of the 16 to simu-  
 late routine monthly practice in the haemodialysis unit. Data  
 115 were collected for the current ESA administrations in the  
 dialysis unit per patient for a period of 4 weeks, i.e. drug,  
 intravenous or subcutaneous, administration dosage per  
 period of 4 weeks, number of administrations per 4 weeks  
 and the number of syringes used per period of 4 weeks.

120

### *Model*

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 A generic model was developed to classify the processes  
 and sub-processes routinely followed in the pharmacy  
 125 (ordering from supplier, receiving and storing and deliv-  
 ering ESA to the dialysis unit) and in the dialysis unit  
 (dose determination, ordering procedure, receipt and  
 storage of ESAs and ESA administration). The processes  
 and activities were modelled on a process modelling  
 130 tool. This model shows the relationship between activities,  
 processes, the functions of the staff involved in the  
 activities, the used documents, and the locations where  
 the activities are performed. Labour costs were derived  
 from actual fully loaded wages of the staff involved in  
 135

\*Aranesp is a registered trademark of Amgen Inc, Thousand Oaks, CA, USA.

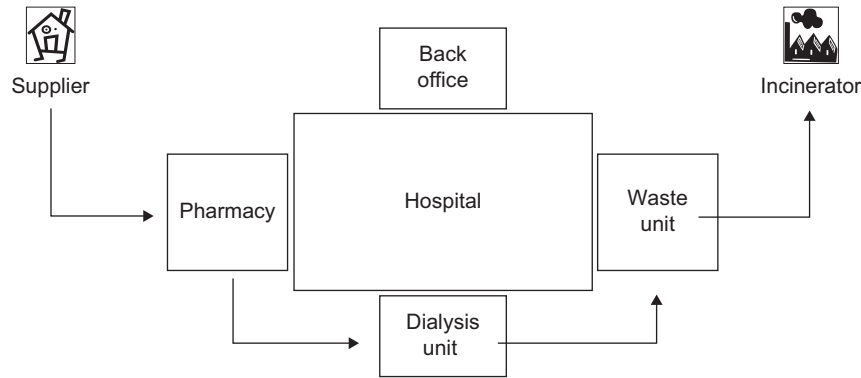


Figure 1. The erythropoiesis stimulating agent delivery process.

Research at the Hospital			
	Interviews and observations	Data collection	Time allocation
What?	<ul style="list-style-type: none"> <li>Assess processes and activities involved in the treatment of anemia</li> <li>Model processes involved in treatments</li> </ul>	<ul style="list-style-type: none"> <li>Retrieve data for calculation of cost reductions:               <ul style="list-style-type: none"> <li>Time savings</li> <li>Material savings</li> </ul> </li> <li>Collect data for:               <ul style="list-style-type: none"> <li>Distribution (ordering from dialysis unit to pharmacy)</li> <li>ESA orders for 52 weeks (pharmacy to supplier)</li> <li>Administration of ESAs for 16 weeks</li> </ul> </li> <li>Pricing of materials               <ul style="list-style-type: none"> <li>Tissues</li> <li>Disinfectants</li> <li>Syringe containers</li> <li>Wages (total cost of employee for hospital)</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>Assess savings in time if Q2W dosing is used</li> <li>Determine time allocation for overall treatment of anemia</li> <li>Determine impact on time allocation when using less frequent dosing</li> <li>Calculate potential time reductions, if any</li> </ul>
How?	<ul style="list-style-type: none"> <li>Study impact of less frequent dosing on models</li> <li>Gather information on qualitative components of study, i.e. operational efficiency</li> </ul>		

Figure 2. Data collection methodology.

138 each activity before being applied to the time required to  
 139 perform each activity. Material costs were drawn directly  
 140 from the facilities' accounting records. The time and  
 materials associated with waste disposal activities were  
 also recorded, as well as the time required in the back  
 office to order ESAs and process invoices and prescriptions.  
 Using the hospital specific data (wages, prices of materials  
 needed at dialysis unit), projections and simulations for  
 the following dosing situations were made: current dosing  
 situation; darbepoetin alfa administered QW; darbepoetin  
 alfa Q2W; darbepoetin alfa once-monthly (QM);  
 epoetin beta administered thrice-weekly (EPO TIW); epoetin  
 beta administered once-weekly (EPO QW) and epoetin  
 beta administered twice-weekly (EPO BIW). For each  
 situation, the current situation dosing data were used as  
 a starting point in the projections and simulations.

*Calculation of cost savings* 154  
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Cost savings were defined as decreases in costs by  
 switching from one dosing situation to another. Two types  
 of cost savings were possible: time savings representing  
 the amount of time and corresponding costs (the time  
 spent during each stage of the ESA delivery process and  
 cost of the staff performing the activities, i.e. wages)  
 gained when switching to another situation, and material  
 savings representing the amount of current costs (number  
 of disinfection tissues, disinfection liquid, hand-wash  
 liquid and sharps bins used in the dialysis unit) with  
 the corresponding cost in case of a switch to another  
 situation. Figure 3 shows how the data were collected  
 and processed to calculate the different savings. Costs  
 were converted to per patient per year.

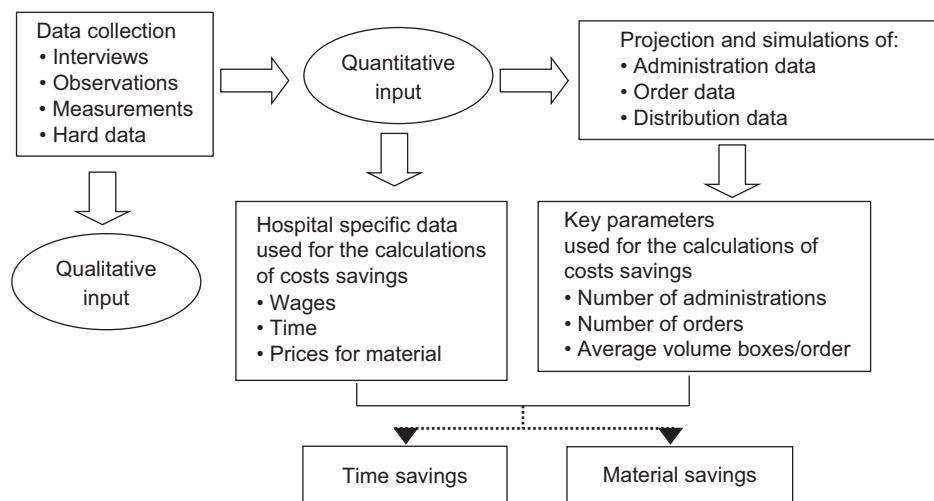


Figure 3.

170 *Statistical analyses*

There were no statistical analyses performed.

175 **Results**
*Current ESA dosing situation in European Hospitals*

180 Altogether we collected data for 2,984 patients treated in 21 hospitals in eight European countries (Belgium, France, Italy, the Netherlands, Spain, Sweden, Switzerland, the UK). The status of the participating centres is described in Table 1. Each centre supplied data for an average of 142 patients (range 42–648). Patients received various ESA dosing regimens (Figure 4); the most common regimen was QW (1,787 patients, 60.0%) and the least common dosing regimen was QM (16 patients, 1.0%).

*Time required for ESA administration process*

189 The mean (SD) time spent preparing ESA administrations in the dialysis unit was 58.5 (36.5) seconds (range 9.8–156.1 seconds per patient per year). The actual time required for ESA injection was a mean of 84.3 (82.2) seconds (range 10.0–209.0 seconds per patient per year).

*Operational costs*

200 The total operational costs of anaemia management varied considerably in the various hospitals, with the total operational costs for 1 year in the current dosing situation ranging between €1,148.39 and €87,464.83 per year (all patients). The total operational costs are mainly determined by the number of patients (e.g., a hospital with 600 patients will have a larger total operational cost

than a hospital with 30 patients, but on per-patient basis the cost can differ). Consequently, the range of total operational costs per patient per year was €13.05–180.70. Various components drive the total operational costs, but time costs were identified as the most important components driving the operational costs. In the current ESA dosing situation, the overall total time cost per patient per year for all of the hospitals varied between €12.74 and €156.89 (min-max); the mean (SD) total time cost per patient for the hospitals was €76.29 (42.82). The total time cost of the processes affected by less frequent dosing was found to be influenced by four factors: number of patients, number of satellites (i.e., small dialysis centres affiliated to the main hospital), dosing frequency and characteristics of the ESA-related processes (driven by the salaries of the person performing the process and the method and time required to carry out the process). The time cost per patient per year in the dialysis units ranged from €10.9 to €154.5 (Figure 5) and this difference in costs can be explained by three of the four influencing components (number of satellites, dosing frequency and process characteristics) since it is a per patient time cost. When we look at a per patient per satellite basis where all units have a Q2W dosing frequency, the difference in time costs is only because of the process characteristic factor (Figure 6).

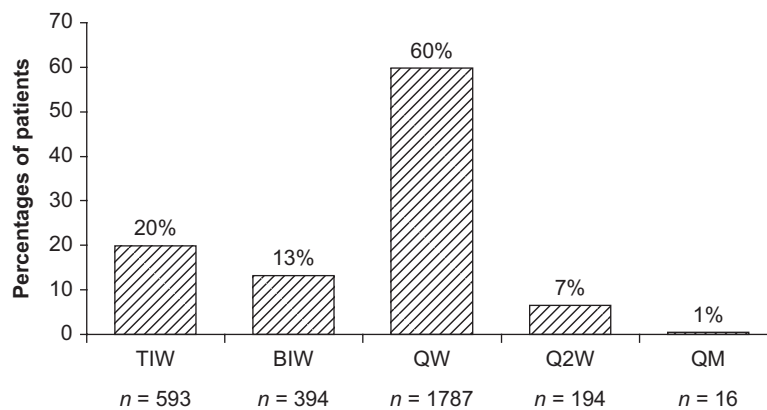
*Impact of less frequent dosing*

235 The impact of the current dosing frequency on the total time costs per patient was of high importance. A large part of the total time costs was allocated to processes driven by the number of ESA administrations. Therefore a hospital where most of the patients receive weekly or Q2W administrations had lower time costs per patient than a hospital where most patients receive ESA either

**Table 1.** Characteristics of the participating centres.

Centre	Number of patients	Status of centre	Darbepoetin alfa		EPO beta		EPO alpha	
			n	(%)	n	(%)	n	(%)
CH 1	83	Academic hospital	35	42	48	58	0	0
CH 2	55	Academic	19	35	36	65	0	0
CH 3	65	Public	21	32	44	68	0	0
CH 4	51	Public	25	49	14	27	12	24
FR 1	648	Private (non-profit)	234	36	297	46	117	18
FR 2	283	Private (non-profit)	283	100	0	0	0	0
BE 1	68	Academic	31	46	37	54	0	0
BE 2	97	Private (non-profit)	0	0	48	49	49	51
BE 3	85	Academic	16	19	20	24	49	58
UK 1	43	Public	43	100	0	0	0	0
UK 2	474	Public	180	38	2	0	292	62
UK 3	327	Public	312	95	8	2	7	2
SE 1	50	Public	27	54	17	34	6	12
SE 2	42	Public	2	5	40	95	0	0
NL 1	88	Private (non-profit)	88	100	0	0	0	0
NL 2	89	Private (non-profit)	89	100	0	0	0	0
ES 1	52	Academic	29	56	0	0	23	44
IT 1	76	Private (profit)	26	34	26	34	24	32
IT 2	148	Public	71	48	13	9	64	43
IT 3	68	Public	19	28	49	72	0	0
IT 4	92	Public	11	12	0	0	81	88
<b>Total</b>	<b>2,984</b>		<b>1,561</b>	<b>52</b>	<b>699</b>	<b>23</b>	<b>724</b>	<b>24</b>

CH, Switzerland; FR, France, BE, Belgium, UK, United Kingdom; SE, Sweden; NE, Netherlands; ES, Spain, IT, Italy. EPO, epoetin.



**Figure 4.** Current dosing frequency in patients with chronic renal disease. TIW: thrice weekly; BIW: twice weekly; QW: once weekly; Q2W: every other week; QM: once monthly

BIW or TIW. In all of the European countries, TIW dosing was associated with a substantially higher pharmacy cost per patient per year compared with Q2W dosing (Figure 7). Dialysis unit costs per patient per year were also higher for patients receiving ESA TIW (Figure 8). Labour was the most powerful cost driver for all dosing regimens in all of the countries, and materials

contributed relatively little to the overall cost in the dialysis unit.

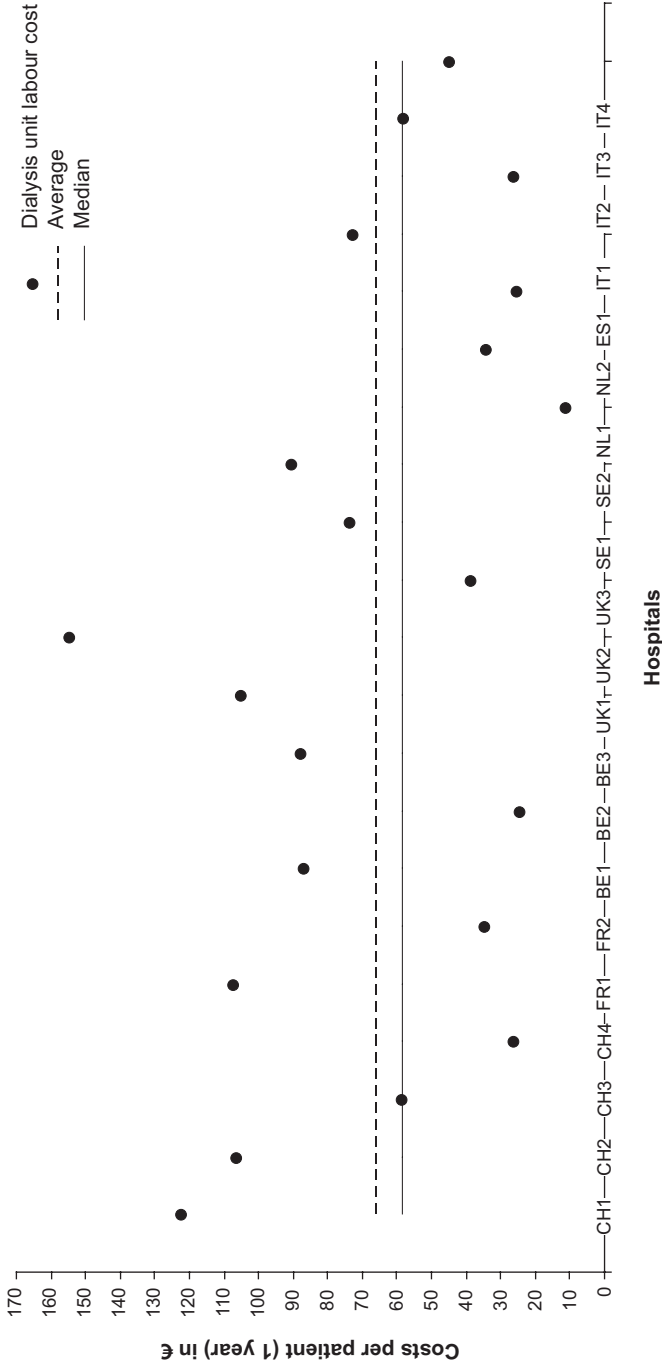
*Cost of using a Q2W ESA regimen*

The mean costs for each process and estimates of the percentage reduction in costs obtainable by using a fixed

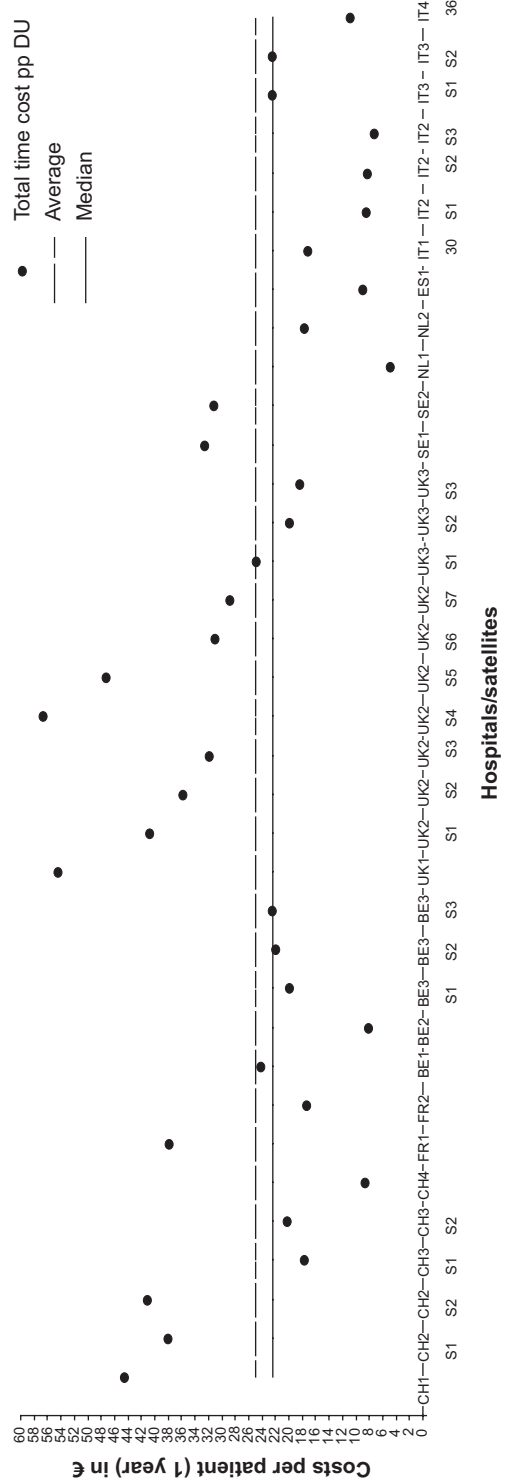
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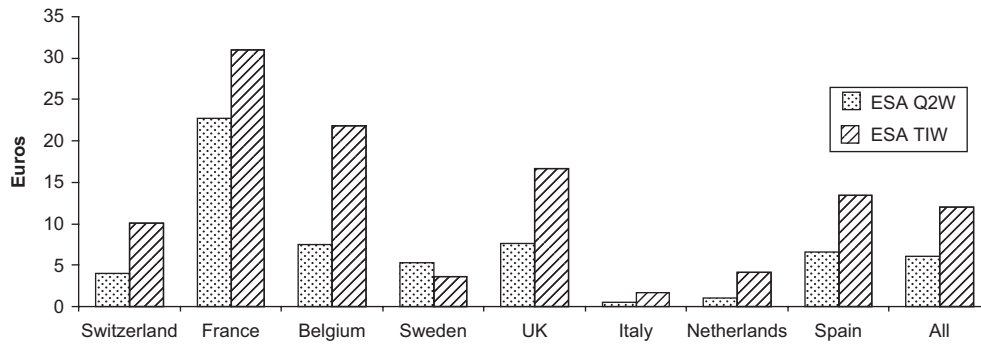
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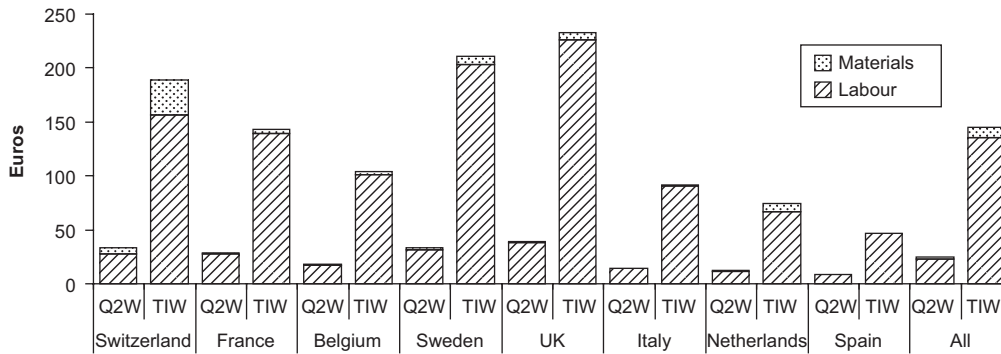
**Figure 5. Dialysis unit labour cost per patient (1 year)\*.**  
 \*Differences between centres may be explained by the influence of the remaining three factors upon coast (number of satellites, dosing frequency, and process characteristics). The impact of the main influencing factor (number of patients) is eliminated since coasts per patient are shown.



**Figure 6. Dialysis unit labour cost per patient (1 year) per satellite in a erythropoiesis stimulating agent Q2W situation.**



**Figure 7. Current pharmacy cost per patient per year\*: Q2W versus TIW.**  
 \*Actual drug cost not included in the calculation.



**Figure 8. Current dialysis unit cost per patient per year\*: Q2W versus TIW.**  
 \*Actual drug cost not included in the calculation.

Q2W ESA administration are summarised in Table 2. By using a fixed Q2W ESA administration, the mean variable costs for each process and the estimates of the percentage reduction in variable costs obtainable, respectively, were: pharmacy labour (€10.1, 39%; range €0.06–42.25 per patient per year); dialysis unit labour (€66.0, 65%; range €10.85–154.5 per patient per year); dialysis unit materials (€4.11, 61%; range €0.00– 48.2 per patient per year) and waste unit materials (€0.43, 49%).

**Discussion**

This study was initiated to assess the operational advantages of less frequent dosing of ESA in terms of cost savings and efficiency advantages. Our results indicate clearly that each hospital has its own unique procedures and costs for administering ESA, and consequently there is substantial variation in the time it takes to perform routine ESA delivery activities in European haemodialysis centres. As expected, besides the cost of drugs, the highest costs associated with ESA delivery are in the dialysis unit (labour costs). Material costs are mainly accumulated in the dialysis unit (disinfection liquid, sharps bins, tissues) and only a relatively small amount in the waste unit.

In this study, switching a patient population to a less frequent dosing interval resulted in the greatest achievable reductions in operational costs because of

the corresponding reduction in ESA administrations required. The largest reductions in the operational costs were observed in labour costs in the dialysis unit. Fewer administrations have a direct impact on the work effort for nurses at an haemodialysis unit. Taking into account the time required to prepare and administer an ESA injection to a patient, a decrease in the number of administrations has a significant impact on labour cost. Fewer administrations also have an effect on the quantity of disinfection liquid, tissues and sharps bins required by the dialysis unit and subsequently result not only in a reduction in material savings but also in an important ecological impact by reducing the amount of waste.

The improved operational efficiency following the switch from epoetin alpha to darbepoetin alfa treatment observed in this study is in agreement with the data reported in other European studies. In the UK, the results of an audit of 82 patients receiving dialysis who were switched from epoetin to darbepoetin alfa showed that the cost of prescribing epoetin was £62 per patient per week compared with £48 per patient per week for darbepoetin alfa – this resulted in yearly savings of £75,000 for the dialysis unit<sup>3</sup>. Similarly, in a Spanish study of 40 patients undergoing dialysis, Ardèvol *et al* reported that switching patients from epoetin to darbepoetin alfa resulted in mean monthly savings of €40.2, €117.5 and €146.3 for 1, 3, and 6 months of treatment, respectively<sup>4</sup>.

**Table 2.** Costs for each process and estimates of the percentage reduction in variable operational costs obtainable by using a fixed Q2W ESA administration in 21 European dialysis centres.

Centre	Current costs per patient per year (€)				Centre	Percentage reduction for Q2W dosing				
	Pharmacy labour cost	Dialysis unit labour cost	Waste unit labour cost	Dialysis unit material cost		Pharmacy labour cost	Dialysis unit labour cost	Waste unit labour cost	Dialysis unit material cost	
CH1	10.32	122.14	0.01	48.15	CH1	20	64	—	64	40
CH2	5.82	106.19	0.00	3.82	CH2	29	62	—	64	70
CH3	5.07	58.29	0.00	3.48	CH3	55	68	—	74	68
CH4	1.82	26.26	0.00	2.20	CH4	18	67	—	0	0
FR1	24.31	107.14	0.00	3.39	FR1	20	65	—	71	65
FR2	39.94	34.46	0.00	0.92	FR2	35	50	—	50	34
BE1	22.59	86.86	0.00	1.93	BE1	61	72	—	74	33
BE2	18.36	24.33	0.00	0.21	BE2	50	67	—	63	63
BE3	8.26	87.53	0.00	1.53	BE3	45	76	—	72	69
UK1	42.25	105.07	0.00	0.83	UK1	49	48	—	45	42
UK2	1.63	154.51	0.00	4.06	UK2	50	75	—	74	68
UK3	0.43	38.66	0.00	3.20	UK3	19	46	—	47	38
SE1	9.96	73.71	0.06	4.59	SE1	14	56	—	43	43
SE2	2.05	90.30	0.00	2.03	SE2	-1	65	—	58	50
NL1	1.89	10.85	0.01	0.17	NL1	53	56	—	0	0
NL2	2.21	33.88	0.00	4.44	NL2	44	48	—	47	35
ES1	11.06	25.38	0.00	0.00	ES1	40	65	—	—	53
IT1	0.00	72.59	0.00	0.00	IT1	—	76	—	—	—
IT2	1.58	25.93	0.00	0.00	IT2	61	70	—	—	72
IT3	2.48	58.09	0.00	0.00	IT3	48	62	—	—	58
IT4	0.06	44.88	0.00	1.29	IT4	8	76	—	71	61
Mean current cost per patient per year (€)	10.10	66.05	0.00	4.11	Mean percentage reduction for Q2W dosing	39	65	—	61	49

CH, Switzerland; FR, France, BE, Belgium, UK, United Kingdom; SE, Sweden; NE, Netherlands; ES, Spain, IT, Italy. Q2W, every 2 weeks; ESA, erythropoiesis stimulating agent.



310 We noted that in hospitals where a lot of manual work  
 is involved in ordering ESA from the supplier, more time  
 savings are possible compared with hospitals where  
 ordering is fully automated. Another factor influencing  
 the amount of time savings is the order procedure. If a  
 315 hospital combines the ESA order with other orders (e.g., to  
 a wholesaler), then the possible savings associated with  
 less frequent dosing tend to be smaller relative to hospi-  
 tals that order ESAs separately. With respect to drug  
 delivery, we found that differences in delivering the ESA  
 320 between the dialysis unit and the pharmacy do not have as  
 big an impact as does the order policy, but nonetheless  
 are not insignificant. If the unit is located next to the  
 pharmacy, then the time savings gained from less fre-  
 quent dosing are smaller than if the pharmacy is situated  
 325 10 miles from the hospital and a transport van is required.

The time savings that can be gained in the dialysis  
 unit by less frequent dosing become more obvious when  
 multi-dose vials are used. With the multi-dose vial, more  
 processes are required by the nurse before the actual  
 330 ESA administration (preparing the multi-dose vial, with-  
 drawal of the individual syringes, additional checking  
 procedures). All of these factors influence the time taken  
 for each ESA administration, and less frequent dosing  
 would result in substantial time gains. In one of the hos-  
 335 pitals, the dosing procedure was affected by a restricted  
 choice of vial sizes. In this particular hospital, only epo-  
 etin alpha and beta were used, of which the pharmacy  
 ordered two dosages of each product. This meant that  
 once a month the nurse had to divide this monthly dosage  
 340 over the weeks of that month. Due to the limited number  
 of dosages ordered, there was no fixed dosing and adminis-  
 tration policy, and dosages as well as administration  
 frequency could differ from week to week. This is an example  
 of how the ESA delivery process can be improved.

344 Another factor affecting the time saving results is the  
 345 obligation in some countries to execute traceability  
 procedures, for example in France. Due to this traceability  
 requirement, some hospitals have extra processes to undergo  
 when ordering and administering ESAs, and less frequent  
 dosing would again lead to extra time savings because  
 350 this procedure would not have to be completed so often.

We discovered that, with the goal of process  
 improvement, hospitals could definitely benefit from  
 sharing best practices with one another. For instance, in  
 the context of disinfection, there were large variations  
 355 in practice. In some hospitals disinfection is a key step in  
 the ESA administration process, while in others there is  
 no disinfection at all prior to ESA administration. Another  
 major difference between the hospitals is the timing of  
 ESA administration during the haemodialysis session, and  
 360 this issue remains unresolved despite substantial clinical  
 debates in the past. In some hospitals, ESA is adminis-  
 tered in the middle of the haemodialysis session. In others,  
 ESA is administered in the first or last hour of the session

or at the end of the dialysis session just before the machine  
 is disconnected. Each hospital has its own motive for the  
 365 timing of administration – some following what is stated in  
 medical journals or as recommended by the ESA supplier  
 or according to hospital policy.

Another interesting observation which became clear  
 from the study is how the process of ordering ESA from  
 370 the pharmacy is organised in the haemodialysis units.  
 Since ESA is prescribed on a monthly basis in most hospi-  
 tals, it is reasonably easy to determine the usage of the  
 haemodialysis centre for 1 week, 2 weeks, or a month. It  
 is therefore surprising to see that many centres do not  
 375 use the prescriptions when determining the quantity for  
 their order to the pharmacy. This can cause over ordering  
 of ESA which may lead to an increased risk of expired  
 goods, and result in additional work because the expired  
 ESAs need to be disposed of and new stock ordered. Other  
 380 hospitals work with a minimum stock principle. If the  
 minimum stock is related to the usage of the haemodialysis  
 unit, this is an efficient way of working, but in most hospi-  
 tals the minimum stock level is static: when prescriptions  
 change, the minimum stock levels are not adjusted to  
 385 this change and this leads to inefficient ordering. In gen-  
 eral, the most efficient way of working for ESA orders is to  
 order based on what is prescribed for that week taking into  
 account a small buffer stock to anticipate possible changes.

During the research in the dialysis units with nurses  
 390 and doctors, one of the issues that came up was the fear  
 of forgetting to administer the drug. Many nurses are  
 concerned that a Q2W dosing schedule would increase  
 the chance of forgetting to administer ESA; moreover,  
 they state that the risk involved in forgetting to administer  
 it is bigger since the dosage administered Q2W is larger.  
 395 There may also be concern that the larger doses of ESAs  
 necessary with Q2W dosing could be associated with  
 397 safety considerations. Extensive research into this topic  
 has not convincingly demonstrated that high doses of  
 ESAs are associated with higher patient morbidity and  
 mortality. In a recently published paper investigating  
 400 the association between cumulative average epoetin  
 dosage and survival in 18,454 patients aged >65 years, it  
 was found that, on average, epoetin dosages of >30,000  
 U/week did not confer additional harm or benefit in  
 elderly haemodialysis patients<sup>7</sup>. In actual fact, it seems  
 that it is ESA hypo-responsiveness which is a strong,  
 405 independent predictor of increased risk of patient mor-  
 bidity and mortality<sup>8</sup>. As a dialysis unit runs on a fixed  
 routine which nurses have followed for years, it is possible  
 that these concerns originate from the fear to change the cur-  
 rent routine. Education and training will be very important  
 in this context to reassure the medical staff involved. 410

The clinical applicability of less frequent dosing for  
 some patients was also one of the worries of some nurses  
 and doctors, but they also acknowledged that, while  
 not universal, a certain percentage of their patient

415 population would benefit from Q2W dosing. The staff  
 also recognised that additional potential beneficial  
 effects associated with less frequent dosing included the  
 reduction in the potential for incorrect doses, less waste  
 from packaging and cooling elements for transport and  
 a reduction in the risk of accidental needle stick injuries.  
 420 In addition, the value of the time savings that could be  
 obtained in the dialysis unit because of less frequent dosing  
 means that extra time can be devoted to patients or other  
 activities, such as training. This may have a positive effect  
 on the quality of care for the patients, the stress level of  
 the nurses and the atmosphere in the haemodialysis  
 unit. Moreover there is a benefit because more staff time  
 425 becomes available due to a switch to Q2W dosing, and  
 this may mean that additional staff may not be required.

Similarly for the pharmacist, less frequent dosing of  
 ESA would reduce the number of inventory activities  
 required and result in time savings that could be directed  
 towards other activities. Meanwhile in the back office,  
 430 although not in direct contact with the patient or the drug,  
 time saving is also enhanced by less frequent dosing  
 because fewer orders need to be placed, deliveries recorded  
 and registration noted for reimbursement purposes.

#### 435 *Limitations of the study*

Acquisition costs of ESAs are only a fraction of the costs  
 to manage anaemia and it should be noted that this  
 study focused exclusively on the operational advantages  
 of less frequent dosing. The operational advantages observed  
 440 in this study are reductions in labour costs, material  
 costs and financial costs. Within this manuscript only the  
 impact on labour and material costs are described, due  
 to the complexity of the financial costs which would  
 have required considerable and lengthy discussion. The  
 combination of the country-specific reimbursement  
 445 system, the payment policy of the ESA suppliers and the  
 hospital's order policy results in an ESA-related financial  
 cost for a hospital. If ESA invoices are paid before the  
 ESA is reimbursed, the hospital has a financial cost (i.e.,  
 pay or lose interest) while in the case of reimbursement  
 before invoice payment, the hospital has a financial benefit  
 450 (i.e., negative cost, earn interest) for the days between  
 reimbursement and payment. In the calculation of this  
 financial cost, price and payment term differences of the  
 ESA administered were not taken into account, and any  
 possible influences of these factors were excluded by  
 converting real ESA prices to a fixed price per microgram.

455 Another possibility of this study could have been to  
 evaluate the benefit for the patient of extending the ESA  
 dosing interval by investigating, for example, the duration  
 of treatment with ESA, the range of haemoglobin values  
 achieved in the patients receiving Q2W dosing and the  
 clinical outcomes of the patients. Unfortunately such

analyses were not possible due to the confidentiality of 460  
 the patient data.

## Conclusion

This was the first comprehensive study to assess the process 465  
 of anaemia management in European haemodialysis  
 centres. Given the high variation in the operational costs  
 between centres due to differences in environmental  
 and structural factors and because practice patterns  
 vary considerably, these results cannot be extrapolated  
 to the practice of dialysis in the United States. Each 470  
 haemodialysis centre should therefore analyse its own  
 cost structure to estimate its potential cost savings. The  
 authors believe that the results of this study may  
 enable a benchmark to be set, and encourage the  
 sharing of information among European haemodialysis  
 centres in an effort to optimise best clinical practice and 475  
 patient care.

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