NICE National Institute for Health and Care Excellence

NICE guidance

Spectra Optia for automatic red blood cell exchange in people with sickle cell disease

Medical technologies guidance

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Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

1 Recommendations

1.1 The case for adopting Spectra Optia for automated red blood cell exchange in people with sickle cell disease who need regular transfusions is supported by the evidence. Spectra Optia is faster to use and needs to be done less often than manual red blood cell exchange.

1.2 NICE recommends collaborative data collection to generate further clinical evidence on some outcomes of treatment with Spectra Optia. In particular, there is a need for long-term data on how automated and manual exchange affect iron overload status and the subsequent need for chelation therapy.

1.3 Based on current evidence and expert advice on the anticipated benefits of the technology when used in people with iron overload, cost modelling shows that in most cases using Spectra Optia is cost saving compared with manual red blood cell exchange or top-up transfusion. The savings depend on the iron overload status of the person being treated and are more likely to be achieved if devices already owned by the NHS can be used to treat sickle cell disease. The estimated cost saving for adopting Spectra Optia is £18,100 per person per year, which has the potential to save the NHS in England £12.9 million each year.

2 The technology

Description of the technology

2.1 The Spectra Optia Apheresis System (Terumo BCT) is an apheresis and cell collection platform which can be used in the treatment of sickle cell disease. The purpose of this evaluation is to assess the use of Spectra Optia for automated red blood cell exchange or depletion-exchange in adults or children with sickle cell disease who are on a transfusion regime. In this procedure, sickle red blood cells are replaced by healthy red blood cells according to a user defined software protocol. The system comprises 3 components: the apheresis machine, embedded software and a single-use blood tubing set. Venous access for Spectra Optia may be through peripheral or central veins. Cannulation of deep peripheral veins or central veins in the neck region or groin may require ultrasound guidance. A permanent indwelling line may sometimes be left in a central vein to avoid the need for repeated cannulations. In a typical exchange procedure, Spectra Optia separates and removes selected components of the blood from the patient using continuous flow and centrifugation. A patented optical detection technology (known as automated interface management) monitors the composition of the blood throughout the procedure. A red blood cell exchange software algorithm is used to calculate the targets for the procedure, and controls the pumps and valves to remove red blood cells. The rest of the blood components (plasma and other cells) are returned to the patient. The device protocol, software and automated interface management system also control the replacement of the removed red blood cells with donor red blood cells. The device has a depletion function, which can reduce the number of circulating red blood cells by replacing a portion of the removed cells with fluid. The procedure typically takes 2 hours to 3 hours.

2.2 Spectra Optia has a CE mark as a class IIb medical device. The Cobe Spectra predecessor system first received a CE mark in 1994 and was also used for this indication. Spectra Optia first received a CE mark in 2007. It is also indicated for bone marrow processing, mononuclear and

granulocyte collection, and therapeutic plasma exchange which are not within the scope of this evaluation.

2.3 The list prices (excluding VAT) for the components of the Spectra Optia system are as follows:

- Capital costs:
  - Spectra Optia device: £45,350
  - Exchange software: £6,700
- Consumables:
  - Spectra Optia exchange set: £1,007 per 6
  - Astotube with injection port: £218 per 50
  - ACD-A anticoagulant (750 ml): £57 per 12
  - Service charge: £4,572 per year.

  Bulk order discounts are available on the consumable sets.

2.4 The company's claimed benefits of Spectra Optia compared with manual red blood cell exchange are:

- Less frequent treatment (that is, exchange with Spectra Optia needs to be done less often).
- Shorter treatment duration.
- Less iron overloading in patients having treatment (so may allow patients to reduce or cease iron chelation treatment).
- Increased patient compliance and efficiency of the procedure.
- Reduced hospital stay and staff time.
- Reduced complications from sickle cell disease leading to reduced hospitalisation and associated treatment.
- The depletion–exchange protocol of the machine makes better use of donor

blood because only the necessary component is used, allowing the remaining blood components to be used in other patients.

Current management

2.5 Existing NICE guidance on managing sickle cell disease addresses patients with an acute painful episode, which is outside the scope of this evaluation.

2.6 The chemotherapy drug hydroxycarbamide is used in people with chronic symptoms of sickle cell disease, but up to 25% of people cannot have or choose not to have it. For example, pregnant and breast-feeding mothers and people planning to conceive should not take hydroxycarbamide.

2.7 Regular elective transfusion programmes are also used to treat sickle cell disease and are the first-line treatment in the primary and secondary prevention of stroke in high-risk individuals. Occasionally, emergency transfusion for acute complications may also be needed. Transfusions may be administered as top-up transfusion or as manual or automated red blood cell exchange. The initial choice of transfusion strategy is likely to depend on a variety of factors including clinical status and the local availability of facilities and services. In general, top-up transfusions are recommended if the main purpose of treatment is to manage anaemia, and if the introduction of transfusions does not pose an unacceptable increase in the risk of vaso-occlusive events, such as stroke. However, top-up transfusions are 'iron positive' and are therefore associated with an accumulation of iron, which will need to be counteracted with chelation therapy (typically after 20 transfusions). Top-up transfusions are commonly used in children who are unlikely to be iron overloaded.

2.8 An alternative to top-up transfusion is red blood cell exchange transfusion. This is considered to be 'iron neutral' because packed red blood cells replace those removed from the patient's blood in an isovolaemic manner. This can be done manually or by using automated systems such as Spectra Optia. Exchange transfusions require larger lines and higher flow rates compared with top-up transfusions, but this is usually achievable via peripheral venous access.

2.9 Iron overload may lead to serious long-term complications. This can be avoided through iron-neutral exchange transfusion or the use of chelation therapy. However, chelation therapies are poorly tolerated by patients; they may cause severe gastrointestinal adverse effects, renal dysfunction, liver dysfunction, arthropathy and decreased white blood cell count. When desferrioxamine is used, this needs to be administered by an overnight infusion pump which is less convenient for patients.

2.10 Regular exchange transfusions are considered to be the best option for patients at high risk of vaso-occlusive events because, unlike top-up transfusion, they do not increase blood viscosity. High-risk patients include those who have had recurrent hospitalisations because of disease complications such as secondary stroke, painful crises, acute chest syndrome and priapism. Patients at high risk of stroke may also be identified through the use of screening tests such as transcranial Doppler.

2.11 Services for people with sickle cell disease vary by region and tend to be concentrated in major cities. Patients outside these areas may have alternative, possibly suboptimal, treatment or need to travel large distances for red blood cell exchange. Almost all patients with sickle cell disease are black or from minority ethnic groups, and all treatment options should be available to people with sickle cell disease to ensure that complications are avoided and a good quality of life is maintained. The NHS England specialised commissioning clinical reference group that advises on this service, F05 Haemoglobinopathies, is currently reviewing service provision across the UK.

3 Clinical evidence

Summary of clinical evidence

3.1 The key clinical outcomes for Spectra Optia presented in the decision problem were:

- percentage of sickle haemoglobin (HbS)
- frequency and length of procedure
- staff time and group or grade needed to perform exchange transfusion
- clinical outcomes
- haematocrit, iron overload and need for chelation therapy
- length of hospital stay for complications
- venous access success rates and device-related adverse events.

3.2 The company carried out 2 separate literature reviews, identifying a total of 33 studies including 4 that only related to adverse events; 30 of these were presented in the company submission. Only 6 of the 30 studies directly compared the Spectra Optia system, or its predecessor the Cobe Spectra system, with manual red blood cell exchange.

3.3 The external assessment centre carried out an additional literature search which identified 31 studies relevant to the decision problem, including 27 that were also identified by the company. It excluded 5 of the 30 studies presented by the company but identified 4 additional studies. Of these studies, the external assessment centre selected 13 for full evaluation. Six were chosen because they compared automated exchange with manual exchange, but they were generally of poor methodological quality (with 3 studies reported as unpublished conference abstracts). An additional 7 single-arm studies that had been published in full in peer-reviewed journals were included: 1 that investigated Spectra Optia and 6 that investigated Cobe Spectra.

Comparative studies

3.4 Cabibbo et al. (2005) reported on a peer-reviewed retrospective observational study in 20 patients with sickle cell disease who had manual or automated red blood cell exchange. In total, the authors reported 206 automated exchange procedures in 13 patients – around 30% (60/206) of which used the Cobe Spectra system and the rest used 1 of 2 other automated systems – and 188 manual exchange procedures in 7 patients. The results reported procedure time, red blood cell (RBC) units used, clinical improvement, iron overload and haemoglobin level of lower than 30% (HbS<30%) achieved, but it was not possible to compare these outcomes with baseline results. The authors concluded that the need for chelation therapy was reduced with automated exchange but that alloimmunisation increased. No statistical analysis comparing automated and manual exchange results was reported.

3.5 Dedeken et al. (2014) reported on a retrospective observational cohort study that was published as a conference abstract. In this study, 10 children (median age 11.8 years) who were having manual exchange (median 1.9 years duration) were switched to automated exchange (Spectra Optia, median 1.7 years). Results were reported separately for Spectra Optia use in years 1 and 2. Median HbS for Spectra Optia was 40% (range 28.5% to 42%) in year 1 and 46% (range 31% to 48%) in year 2 compared with 33.5% across both years (range 25% to 42%) for manual exchange (p=0.0002). The median length of procedure for Spectra Optia was 87.3 minutes and 91.0 minutes in years 1 and 2 respectively, compared with 245 minutes for manual exchange (p=0.0002). The average interval between procedures for Spectra Optia was 34 days and 42 days for year 1 and year 2 respectively compared with 28 days for manual exchange (p=0.0002). Spectra Optia used 32.2 ml/kg and 30.0 ml/kg body weight of packed RBC in year 1 and year 2 respectively, compared with 18.3 ml/kg used in manual exchange (p<0.0001). In terms of total RBC units used, Spectra Optia used 67.0 and 65.5 in year 1 and year 2 respectively, compared with 39.5 used in manual exchange (p<0.0001).

3.6 Duclos et al. (2013) reported on a retrospective case-matched study that was published as a full article in a peer-reviewed journal. In the study,

5 children (average age 12 years) from different treating centres had exchange with the Cobe Spectra system (60 procedures). These were matched, through weight and age, with children (average age 11 years) from a different centre who had manual exchange (124 procedures). The authors reported baseline patient data before the procedure, but post-procedural data were not available. The transfused blood volume for treatment with Cobe Spectra was higher than that with manual exchange, at 41 ml/kg (95% confidence interval [CI] 19.6 to 60.0) compared with 11.1 ml/kg (95% CI 6.6 to 20.0).

3.7 Fasano et al. (2015) reported on a retrospective observational study that was published as a conference abstract and was not peer reviewed. The study aimed to compare the efficacy of different procedures in reducing ferritin and liver iron content. Three procedures were used: simple transfusion (top-up transfusion, 20 patients), partial transfusion (details of procedure not reported, 6 patients) and automated exchange (system presumed Spectra Optia as stated by company, 10 patients). To be eligible, the patients needed to have a minimum of 6 months' haematological data, but these data were not reported in the abstract. Changes in ferritin and iron content were reported as well as average HbS and alloimmunisation rates. For automated exchange, the average HbS was 36% with an average ferritin change of -61 ng/ml/month (range -161 to 17). For partial transfusion, the average HbS was 34%, with an average ferritin change of 19 ng/ml/month (range -42 to 106).

3.8 Kuo et al. (2015) reported in a letter on a retrospective cohort study that was the only comparative study conducted in the UK, in 2 London centres. The aim of the study was to investigate 'whether adult sickle cell disease patients on manual exchange differ from those on automated exchange in their ability to achieve predefined haematological targets, rate of complications, blood usage and clinical outcomes over a 1-year period'. The study investigated 1 group (n=30) who had Spectra Optia for chronic sickle cell disease in 1 centre, and another group (n=21) who had manual exchange in another. The patients at each centre were not matched but were well described with no differences reported in demographics, primary indications or chelation status. However, patients having manual exchange were significantly younger than those having automated exchange with Spectra Optia (median 23 years compared

with 31 years, p=0.035), and manual exchange was administered more frequently through a peripheral venous route rather than a central route (p<0.0001). The outcomes reported in the study included:

- mean pre-procedure HbS: 50% (95% CI 27% to 76%) Spectra Optia compared with 55% (95% CI 16% to 72%) for manual exchange (p=0.162)
- number of patients who had less than two-thirds of procedures within the HbS target: 19 out of 30 Spectra Optia and 19 out of 21 for manual exchange (p=0.048)
- median post-procedure haematocrit: 0.31 (0.23 to 0.35) for Spectra Optia and 0.31 (0.25 to 0.38) for manual exchange (p=0.931).

Resource use was also measured: average packed RBC utilisation was 55 units per patient per year for Spectra Optia and 31 for manual exchange. Procedure time was 127 minutes for Spectra Optia and 241 for manual exchange, and mean procedure intervals were 6.66 weeks for Spectra Optia and 4.86 weeks for manual exchange. Peripheral venous access was only achieved in 1 of the 30 patients in the Spectra Optia arm, whereas it was achieved in 14 of 21 patients in the manual exchange arm. Top-up transfusions were needed in 11 procedures in the manual exchange arm, but in no patients in the Spectra Optia arm.

3.9 Woods et al. (2014) reported on a retrospective observational study that was published as a conference abstract and was not peer reviewed. In this study data were collected from 38 patients in a single institution over 2 years. The number of procedures was not reported, but in the first year 5 patients had automated exchange (confirmed to be with Spectra Optia by the company), 17 had manual exchange and 16 had both. In the second year, 13 had automated red blood cell exchange and 25 had manual exchange, but results for this year were not presented separately. Patients were actively selected for Spectra Optia based on age and size, and could choose not to have Spectra Optia. Outcomes reported in the study included: proportion of procedures achieving HbS targets (0.80 [95% CI 0.40 to 1.00]) for automated exchange and 0.50 [interquartile range 0.28 to 0.90] for manual exchange, p=0.27; ferritin concentrations 875 ng/ml [interquartile range 578 ng/ml to 2,659 ng/ml] for automated exchange and 1,527 ng/ml [interquartile

range 731 ng/ml to 568 ng/ml] for manual exchange, p=0.56) and catheter complications (seen in 15 of 21 patients having automated exchange and in 1 of 17 having manual exchange).

Single-arm studies

3.10 Quirolo et al. (2015) reported on a prospective multicentre study that was published in a peer-reviewed journal. The external assessment centre highlighted this study because it investigated Spectra Optia and was of a relatively high methodological and reporting standard. Patients (adults and children over 12 years age) were enrolled to have either standard exchange or automated exchange/deletion exchange with Spectra Optia. 72 patients were enrolled in the study, 60 of whom were evaluated for efficacy. Only 1 procedure was reported per patient. The prespecified primary end point was Spectra Optia's ability to accurately achieve targets for the fraction of a patient's original red cells remaining, which was reported as 0.90 (range 0.17; acceptable range defined as 0.75 to 1.25) in the evaluable population. The mean procedure time (and standard deviation) for the evaluable population was 90 minutes (range 22); for standard automated exchange this was 92 minutes (range 24), compared with 86 minutes (range 16) for depletion exchange. The procedure time was statistically significantly longer in adults (95 minutes [range 24]) than in children (81 minutes [range 16]). The mean volume of replacement blood used in all procedure types was 1,895 ml (range 670); this was also statistically significantly higher for adults (2,118 ml [range 702]) than for children (1,449 ml [range 260]). Depletion exchange needed less blood (1,562 ml [range 281]) than standard exchange (2,016 ml [range 729]), and this difference was statistically significant (although did not result in fewer units used).

3.11 Bavle et al. (2014) reported on a retrospective analysis that was published as a full article in a peer-reviewed journal. The study analysed the physical growth of children with sickle cell disease (a secondary outcome in the decision problem) who had regular exchange. The study compared the height, weight and BMI of 36 patients before and after long-term exchange with 2 control groups: all patients with sickle cell disease were from the Cooperative Study of Sickle Cell Disease (CSSCD), and a subset of 64 matched controls taken from CSSCD. The

patients showed a significant increase in height, weight and BMI after long-term exchange ($p \leq 0.0001$). There was also a significant increase in weight, height and BMI compared with the matched controls from the CSSCD and the entire CSSCD cohort ($p<0.01$).

3.12 Billard et al. (2013) reported on a retrospective case series that was published as a full article in a peer-reviewed journal. All patients had automated exchange using the Cobe Spectra system. The study comprised 18 children having 443 procedures through a short-term, indwelling, double-lumen catheter, with a follow up of 6.5 years. Due to the descriptive nature of this case series, results were described on an individual patient basis only using a before-and-after analysis (Wilcoxon signed rank test), which was subject to confounding and bias.

3.13 Kalff et al. (2010) reported on a retrospective case series that was published as a full article in a peer-reviewed journal. All patients had automated exchange in the same centre using the Cobe Spectra system. The study included 13 adult patients and evaluated the effectiveness of a regular exchange programme. Patients had red blood cell exchange through a peripheral venous cannula or arterio-venous fistula, initially every 4 weeks and then every 4 to 6 weeks. End points included pre and post-procedure HbS (mean pre-procedure 47.4% [range 40.7% to 59.3%], mean post-procedure 25.5% [range 18.5% to 32.6%]), incidence of sickle cell-related acute events, and the progression of pre-existing related end-organ damage and development of new end-organ damage. The regular exchange programme reduced HbS levels to the target of less than 30% immediately after the procedure in all but 2 patients. A total of 16 acute sickle-related events occurred in 5 patients in 846 cumulative months of patient follow up. No patient experienced stroke or multi-organ crises, evidence of new end-organ damage or progression of pre-existing related end-organ damage. Ferritin levels were monitored in 11 patients. In patients with normal baseline levels, these were maintained whereas in patients with slightly higher baseline levels they were reduced without chelation therapy.

3.14 Masera et al. (2007) reported on a retrospective review that was reported as a full article in a peer-reviewed journal. This was an 11-year review of routine data from a cohort of 34 patients with sickle cell

disease in 1 hospital. The authors focused on 13 high-risk patients and reported efficacy, safety and cost outcomes of a periodic regimen of erythro-exchange with the Cobe Spectra. Outcomes included change in HbS and ferritin levels, hospital admissions and painful crises. The authors reported a reduction in all of these outcomes compared with data before erythro-exchange was started, but the reported changes were not tested for statistical significance.

3.15 Sarode et al. (2011) reported on a retrospective review that was published as a full article in a peer-reviewed journal. This study is a review of a 2-phase automated exchange method using isovolaemic haemodilution with conventional red blood cell exchange (C-RBCX), compared with the C-RBCX protocol alone. In the study, 14 patients having the automated exchange protocol (using the Cobe Spectra device) were compared with 6 historical controls having C-RBCX, and outcomes focused on resource use. The authors reported an increase in haematocrit (pre-procedure 27.8% [range 2.4], post-procedure 32.8% [range 1.6]) and a decrease in HbS (pre-procedure 41.8% [range 6.1], post-procedure 9.8% [range 2.4]) following the automated exchange protocol; the changes were not tested for statistical significance. C-RBCX procedures needed 39.5 ml/kg (range 4.6) packed RBC, lasted 107.3 minutes (range 6.7) and were done every 37 days (range 7.0), leading to 7 procedures per year.

3.16 Shrestha et al. (2015) reported on a retrospective observational cohort study that was published as a full article in a peer-reviewed journal. The study was designed to compare 2 methods of vascular access (dual lumen port valves with temporary central venous and peripheral catheters) during automated exchange with the Cobe Spectra system. They reported outcomes including inlet speed, duration of procedures and rates of complications. Twenty-nine adults with sickle cell disease who had a total of 318 procedures were included for analysis. The authors reported a mean duration of 2.0 hours (range 1.6) for the procedure and a mean number of blood units used of 6.3. They also reported 87% and 95% success rates for the post-procedure haematocrit and HbS targets respectively.

Committee considerations

3.17 The committee considered that there were limitations in the clinical evidence, meaning that not all of the outcomes defined in the scope could be evaluated. However, it was advised that this was partly because of limitations in study methodologies, mainly as a result of a lack of clinical equipoise in treatment modalities and the need for personalised treatment in individual patients with sickle cell disease. Nonetheless, the committee concluded that the evidence together with expert advice was sufficient to accept that Spectra Optia offers significant clinical benefits compared with manual exchange or top-up transfusion. The committee noted that automated exchange procedures are shorter and have a longer-lasting clinical benefit than manual exchange, meaning that patients need the procedure less often.

3.18 The committee noted that the evidence did not show significant differences in reducing iron overload in patients having automated exchange with Spectra Optia compared with patients having manual exchange. It was advised by the clinical experts that exchange transfusion was the best treatment option for avoiding iron loading in people with sickle cell disease. The committee concluded that long-term data should be collected on how automated exchange affects iron overload status and the need for chelation therapy.

3.19 The committee was informed by the clinical experts that, in practice, manual red blood cell exchange is not iron neutral. It was advised that the level of precision needed to achieve absolute iron neutrality is not possible in a typical hospital setting or within a reasonable procedure time using the manual technique. However, the experts advised that use of Spectra Optia automated red blood cell exchange can achieve levels of precision that mean that iron neutrality can be maintained.

3.20 The committee noted that optimal iron management is very important in people with sickle cell disease. Iron chelation therapy can be used to avoid the serious complications of iron overload, but the committee was advised that this treatment is poorly tolerated and compliance is therefore low. Oral iron chelators are unpalatable and chalky and infusion pump chelators must be administered overnight and on a frequent basis.

The committee accepted expert advice that Spectra Optia is the only reliably iron-neutral transfusion therapy currently available, and that this is particularly important as chelation therapy is costly and poorly tolerated.

3.21 The committee was advised that venous access can be difficult for patients having exchange procedures, particularly in very young children (the clinical experts informed the committee that most children having Spectra Optia were over 10 years old). Experts advised that safely achieving vascular access is an important factor in adopting Spectra Optia and that this may depend on the availability of appropriately trained staff. A patient expert added that vascular access was a source of considerable anxiety for some patients before transfusion sessions. The committee was advised that there is an inequity of access to specialised venous access teams and that this may affect uptake of the Spectra Optia system. The skills needed to use Spectra Optia are transferable, so staff are able to use the device for other clinical indications.

4 NHS considerations

System impact

4.1 Adopting Spectra Optia is claimed to have a range of system benefits (see section 2.4). Published evidence was presented on procedure times and treatment intervals (see section 3.16) but not on the other outcomes.

4.2 Clinical experts informed the committee that Spectra Optia may be operated by 1 appropriately trained nurse. In larger units with more than 1 machine, 1 nurse can potentially manage 2 patients having exchange procedures at the same time. The company provides initial and refresher training at no additional cost. Operator competency may be more difficult to maintain in areas with low numbers of patients.

4.3 Spectra Optia is a multifunctional device and is already in use at many hospitals for other indications. The low prevalence of sickle cell disease in some parts of the UK means that existing Spectra Optia devices could be made available as part of a device-sharing scheme. The external assessment centre developed a scenario which explored the costs and benefits of this.

Committee considerations

4.4 The committee discussed the current lack of consistency in services for people with sickle cell disease. Most people with the disease live in major urban centres, so services in cities must be able to provide for a large sickle cell population. In contrast, in rural areas there may be only a small number of people with sickle cell disease. The clinical experts advised that around 75% of sickle cell patients are based in London, with significant populations in both Manchester and Liverpool. The committee was made aware that a review of services in England is being carried out by the NHS's clinical reference group advising on haemoglobinopathy (F05 Haemoglobinopathies) to ensure that there is 1 designated centre for each geographical area.

4.5 The committee noted that automatic exchange with Spectra Optia uses more packed red blood cell units than manual exchange, even taking into account the longer interval between procedures.

4.6 The committee noted that current levels of tariff remuneration may serve as a disincentive to the use of this technology. The committee was also advised by clinical experts that there is currently inequity of access to treatment with Spectra Optia and that the devices are more often used for other conditions and not necessarily offered to patients with sickle cell disease.

5 Cost considerations

Cost evidence

5.1 The company identified 7 studies from the clinical evidence search which incorporated an economic analysis. However, it was unable to draw any firm conclusions from these studies. The external assessment centre did not identify any additional economic evidence and agreed with the company that these studies did not provide relevant information.

5.2 The company presented an economic model comparing Spectra Optia with manual exchange. It also included top-up transfusion as a comparator in the model, although this was not specified in the scope decision problem. The population was considered as 12 subgroups based on a mixture of age, clinical indication and degree of iron overload to represent the heterogeneous case-mix of patients with sickle cell disease and their differing clinical needs and associated costs. The disease complications considered were secondary stroke, painful crises, acute chest syndrome and priapism. The population groups were:

- Children at high risk of primary stroke, with and without iron overload (mild, moderate and severe).
- Children having treatment to prevent complications of sickle cell disease, with and without iron overload.
- Adults having treatment to prevent complications of sickle cell disease, with and without iron overload.

The structure was a simple costing model which simulated the 'average' cost of chronic sickle cell disease treatment for 1 patient using 1 of 3 modalities: automated exchange with Spectra Optia, manual exchange or top-up transfusion. The time horizon of the economic model was 5 years.

In the absence of published data relating specifically to the Spectra Optia system, the clinical parameters used in the company's model (table 1) were

based on clinical expert opinion, extrapolations from the clinical evidence and data from UK registries and NHS audits. The cost of iron overload was the main driver for the cost of treatment in the company's model.

Table 1 Clinical parameters used in the company's model

Parameter	Spectra Optia	Manual exchange	Top-up transfusion
Patients with iron overload	0%	10%, 30% and 50% after 24 months, 36 months and 48 months	90% after 12 months
Patients able to cease chelation therapy	Mild iron overload: 50% and 100% after 12 months and 24 months Moderate iron overload: 5%, 15%, 30% and 50% after 12 months, 24 months, 36 months and 48 months Severe iron overload: 5%, 15% and 30% after 24 months, 36 months and 48 months	N/A, iron overload does not decrease in this arm	N/A, iron overload does not decrease in this arm
Yearly rate of hospital admissions	Children and adults (complications): 0.65 Children (stroke): 0.00	Children and adults (complications): 1.1 Children (stroke): 0.01	Children and adults (complications): 1.1 Children (stroke): 0.07
Procedure time	Adults: 110 minutes Children: 86 minutes	245 minutes	Adults: 300 minutes Children: 180 minutes
Procedures per year	8.5	12	13

Parameter	Spectra Optia	Manual exchange	Top-up transfusion
Packed RBC units per procedure	Adults: 7 Children: 5	4	2
Staffing	1 grade 5	1.5 'highly qualified'	0.5 grade 5

Abbreviations: RBC, red blood cell; N/A, not applicable.

5.3 Parameters relating to adverse events and alloimmunisation were not included as they were considered to be similar for all modalities. The cost of secondary stroke was taken from Cherry et al. (2012) and set as a one-off payment of £21,807 at 2.5 years (3 months of acute costs and 2.25 years of ongoing care costs); there were insufficient data to support differences in rates of primary stroke between transfusion modalities. The cost per hospital admission included was £1,354, taken from NHS reference costs. Chelation therapy costs were calculated from British national formulary values using average body masses and assumed to be £21,022 per patient per year for adults and £9,954 for children. The cost per packed red blood cell unit was £120 as listed in NHS reference prices. The Spectra Optia exchange set was the only consumable that was not common across all modalities, for which the company used its list price (£167.84).

5.4 The company did 8 univariate deterministic analyses for each of the 12 subgroups. These tested sensitivities to: stroke timing and severity, hospital admissions, cost of medication, staff grades, staff ratios, red blood cell units, procedure length and frequency, and the cost of consumables. Where a parameter change altered the ranking of modalities, threshold analyses were done to inform when the modality orderings changed. The values used for these analyses were informed by values taken from published clinical evidence, clinical advisers, and company and reference sources. The company also did 4 scenario sensitivity analyses: use of depletion exchange protocol with Spectra Optia, resulting in a reduction in the number of packed red blood cell units used in automated exchange by 1; mild iron overload with low chelation costs; severe iron overload with high chelation costs; and an

increased rate of patients ceasing chelation therapy for moderate and severe iron overload when having automated exchange.

5.5 The results of the company's base case showed that the Spectra Optia system was always cost saving compared with manual exchange, with savings over 5 years ranging from £360 per adult patient with severe iron overload to £52,516 per adult patient with mild iron overload. The absolute costs of treating sickle cell disease in adult patients over the 5-year time horizon varied from £48,093 for Spectra Optia in the absence of iron overload to £128,670 for manual exchange in those with iron overload.

5.6 The sensitivity analyses showed that the Spectra Optia system was sensitive to changes in procedural costs (in particular the need for packed red blood cells), and that top-up transfusion was sensitive to changes in chelation costs. Manual exchange had higher procedural costs than top-up transfusion (through staff time and grade, and greater need for red blood cell units) and higher chelation costs than Spectra Optia, and was rarely the lowest cost modality. Stroke and emergency hospital admissions had little impact in the sensitivity analyses except in some extreme threshold scenarios.

Additional work by the external assessment centre

5.7 The external assessment centre revised some input parameters of the model concerning capital, procedural and chelation costs to reflect values which it considered were more plausible. However, it judged that the limited clinical evidence (and the associated uncertainty) should remain a key consideration when interpreting the results.

5.8 The company's model did not include capital costs (£52,052) or maintenance costs (£4,572 per year) for Spectra Optia, although it did report separate analyses on these costs. The external assessment centre considered it wrong to exclude these costs from the model, and so created scenarios to reflect the mixed use functionality of the technology and relatively low demand (due to low prevalence of sickle cell disease) in some areas of the country. The external assessment centre determined that treating 30 sickle cell patients per year would use 50%

capacity of each Spectra Optia system, and 15 patients per year would use 30% of capacity. The external assessment centre also included sensitivity analyses in which 100% of the device's capacity was used exclusively for treating sickle cell disease (with patients incurring the full cost) or where 50% of capacity was used elsewhere. In these analyses, the external assessment centre also extended the lifespan of the device from 5 years to 7 years.

5.9 The external assessment centre also noted that the cost of chelation therapy in the company's model did not include diagnostic and monitoring costs. An estimate of the chelation costs used in the model for the monitoring of iron overload was provided in confidence to the committee. The proportion of patients having chelation therapy after top-up transfusion in years 2 to 5 of the model was 90%. These patients entered the model with no iron overload. The external assessment centre revised this value to 75% based on 250 of 332 patients in the Haemoglobinopathy Registry Report having regular chelation therapy (Foster 2014).

5.10 The company had also assumed that adults and children having manual exchange procedures would both need 4 units of packed red blood cells. The external assessment centre reduced this to 3 units in children. Similarly, the procedure time for manual exchange in children was reduced from 254 minutes to 208 minutes. The number of staff needed per patient for manual exchange was also reduced from 1.5 to 1.0, following expert advice.

5.11 Results from the economic modelling showed that:

- For 30 patients having automated exchange per year at 100% use of the device's capacity, Spectra Optia is cost saving compared with manual exchange in all patients with mild iron overload and in adults without iron overload.
- For 30 patients having automated exchange per year at 50% use of the device's capacity, Spectra Optia is cost saving compared with manual exchange in all patients with no or only mild iron overload, and in adults with moderate iron overload.

- For 15 patients having automated exchange per year at 100% use of the device's capacity, Spectra Optia is cost saving compared with manual exchange in all patients with mild iron overload.
- For 15 patients having automated exchange per year at 50% use of the device's capacity, Spectra Optia is cost saving compared with manual exchange in all patients with mild iron overload, adults with no iron overload, and children with no iron overload having treatment for the secondary prevention of stroke only.

5.12 The committee asked the external assessment centre to make some additional changes to the model. In the company's model, 90% of patients were assumed to have iron overload when beginning treatment with Spectra Optia (and were therefore having chelation therapy) whereas only 80% had iron overload when beginning manual exchange. The company provided no rationale for this difference so the external assessment centre set chelation treatment rates at 90% for both Spectra Optia and manual exchange.

5.13 The external assessment centre decided that it would be most helpful if the cost modelling included a range of scenarios reflecting device-sharing schemes. The external assessment centre included scenarios for 30 patients using the device at 100% capacity (and so 100% of its capital cost), 50% capacity and 0% capacity (for centres that already have the device but do not use it for red blood cell exchange). From the external assessment centre's subsequent changes to the model, the committee concluded that Spectra Optia is cost saving in the following scenarios:

- 0% capital cost attributed to sickle cell disease: Spectra Optia is cost saving in all patients except when compared with top-up transfusion in patients with severe iron overload, and transfusion for preventing stroke in children with moderate iron overload.
- 50% capital cost attributed to sickle cell disease: Spectra Optia is cost saving in all patients with no or mild iron overload, and in some patients with moderate and severe iron overload.
- 100% capital cost attributed to sickle cell disease: Spectra Optia is cost saving in all patients with mild iron overload, in some patients with no iron overload, and in adults with moderate iron overload. These results are summarised in

table 2 and table 3.

Table 2 External assessment centre's revisions to company model (automated compared with manual)

Scenario (capital costs attributed to SCD) and population	No overload	Mild overload	Moderate overload	Severe overload
0%: adults	-£25,011	-£96,512	-£24,874	-£10,867
0%: children (secondary prevention)	-£12,439	-£46,294	-£12,374	-£5,742
0%: children (primary prevention)	-£10,005	-£43,860	-£9,940	-£3,307
50%: adults	-£16,555	-£88,056	-£16,418	-£2,410
50%: children (secondary prevention)	-£3,983	-£37,838	-£3,918	£2,715
50%: children (primary prevention)	-£1,548	-£35,404	-£1,484	£5,149
100%: adults	-£8,099	-£79,600	-£7,961	£6,046
100%: children (secondary prevention)	£4,474	-£29,382	£4,539	£11,171
100%: children (primary prevention)	£6,908	-£26,947	£6,973	£13,605

Abbreviations: SCD, sickle cell disease. Negative values indicate cost savings with Spectra Optia.

Table 3 External assessment centre's revisions to company's model (automated compared with top-up)

Scenario (capital costs attributed to SCD) and population	No overload	Mild overload	Moderate overload	Severe overload
0%: adults	-£77,483	-£81,493	-£9,855	(£4,152)
0%: children (secondary prevention)	-£35,424	-£37,322	-£3,402	(£3,230)
0%: children (primary prevention)	-£31,681	-£33,580	£341	(£6,973)
50%: adults	-£69,027	-£73,037	-£1,399	(£12,609)
50%: children (secondary prevention)	-£26,967	-£28,866	£5,054	(£11,687)
50%: children (primary prevention)	-£23,224	-£25,123	£8,797	(£15,430)
100%: adults	-£60,571	-£64,581	£7,058	(£21,065)

Scenario (capital costs attributed to SCD) and population	No overload	Mild overload	Moderate overload	Severe overload
100%: children (secondary prevention)	-£18,511	-£20,409	£13,511	(£20,143)
100%: children (primary prevention)	-£14,768	-£16,667	£17,253	(£23,886)

Abbreviations: SCD, sickle cell disease. Results in brackets are considered clinically unlikely. Negative values indicate cost savings with Spectra Optia.

5.14 The results show that Spectra Optia is cost saving compared with manual exchange and top-up transfusion in most patients with sickle cell disease. The highest cost savings are £96,512 (compared with manual exchange) and £81,493 (compared with top-up transfusion) per patient per year for adults with mild iron overload where an already functioning and purchased device can be used. The lowest cost savings are £1,484 (compared with manual exchange for primary prevention in children with moderate iron overload when the device has been procured at 50% of the capital cost) and £1,399 (compared with top-up transfusion in adults with moderate iron overload) per patient per year.

5.15 Spectra Optia is cost incurring compared with manual exchange for children with severe iron overload if the device is procured at 50% of the capital cost. If the device is purchased at 100% of the capital cost, it is cost incurring (at £2,715 to £13,605 per patient per year) compared with manual exchange for children with no or moderate iron overload and for all patients with severe iron overload. Using Spectra Optia is also cost incurring compared with top-up transfusion in some patients with moderate and severe iron overload. However, this comparator is considered to be a clinically poor treatment option for these patient groups and it is unlikely that it would be the preferred treatment option for people with iron overload.

Committee considerations

5.16 The committee considered that local providers should take into account the availability of existing devices when planning services for people with sickle cell disease; the potential for device-sharing schemes was discussed and these were represented in the revised cost modelling

carried out by the external assessment centre.

5.17 The committee noted that the levels of iron overload in patients included in the model were not clearly defined. The company's cost model stated that these were based on serum ferritin levels but no ranges were provided for the mild, moderate and severe categories used. The expert advisers informed the committee that there were no routinely used and agreed values for this classification.

5.18 The committee noted that top-up transfusion was not included as a comparator in the scope because it is generally used to treat anaemia and emergency crises in patients with sickle cell disease. Top-up transfusion is not suitable as a long-term regime because it is iron positive, and so is not an appropriate current standard comparator for automated exchange. However, several clinical experts stated that top-up transfusion is sometimes used as a long-term therapy in hospitals where provision of treatments for sickle cell disease is limited, or in patients who have disease complications that preclude the use of exchange transfusions (such as poor venous access).

5.19 The committee noted that many values in the cost model for Spectra Optia are based on estimates. In particular, it was not possible to define the different categories of iron overload used in the model in terms of serum ferritin levels (or any other kind of measurement of iron).

5.20 Having noted these uncertainties, the committee concluded that Spectra Optia would be cost saving for most patients compared with manual exchange and top-up transfusion.

6 Conclusions

6.1 The committee concluded that Spectra Optia is effective for red blood cell exchange in managing sickle cell disease. It noted that automated exchange with Spectra Optia is needed less frequently and is quicker than manual exchange. The committee noted that automated exchange is considered by experts to be the only reliably iron-neutral transfusion therapy available, and that this is particularly important because chelation therapy is costly and poorly tolerated. Using Spectra Optia in patients with iron overload will not increase serum ferritin levels, and may decrease levels with prolonged treatment.

6.2 Using Spectra Optia is likely to result in significant cost savings in most patients with sickle cell disease. There are uncertainties in the cost model because of the absence of robust published data estimates for some outcome measures, and the need to incorporate qualitative information advised by experts. Cost savings may be maximised through device-sharing schemes and by avoiding iron overload and the subsequent use of chelation therapy.

6.3 The committee noted the need for high-quality clinical data collection on the outcomes of treatment with this technology. In particular, long-term data are needed on how automated and manual exchange affects iron overload status and the subsequent need for chelation therapy. These data could be used to address the residual uncertainties about the use of Spectra Optia.

7 Committee members and NICE lead team

Medical technologies advisory committee members

The medical technologies advisory committee is a standing advisory committee of NICE. A list of the committee members who took part in the discussions for this guidance appears below.

Committee members are asked to declare any interests in the technology to be evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each medical technologies advisory committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Dr Peter Groves (Chair)
Consultant Cardiologist, Cardiff and Vale University Health Board

Ms Susan Bennett
Lay member

Mr Matthew Campbell-Hill
Lay member

Professor Daniel Clark
Head of Clinical Engineering, Nottingham University Hospitals NHS Trust

Dr Fiona Denison
Reader/Honorary Consultant in Maternal and Fetal Health, University of Edinburgh

Professor Tony Freemont
Professor of Osteoarticular Pathology, University of Manchester

Professor Shaheen Hamdy
Professor of Neurogastroenterology, University of Manchester

Dr Cynthia Iglesias
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Professor Mohammad Ilyas
Professor of Pathology, University of Nottingham

Dr Greg Irving
GP and Clinical Lecturer, University of Cambridge

Professor Eva Kaltenthaler
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Dr Paul Knox
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Senior Lecturer and Honorary Consultant Physician in Rehabilitation Medicine, University of Leeds

Dr Jai V Patel
Consultant Vascular Radiologist, Leeds Teaching Hospitals NHS Trust

Mr Brian Selman
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Professor Allan Wailoo
Professor of Health Economics, School of Health and Related Research (ScHARR), University of Sheffield

Mr John Wilkinson
Director of Devices, Medicines and Healthcare Products Regulatory Agency

Professor Janelle Yorke
Lecturer and Researcher in Nursing, University of Manchester

Dr Amber Young
Consultant Paediatric Anaesthetist, Bristol Royal Hospital for Children

NICE lead team

Each medical technology assessment is assigned a lead team of a NICE technical analyst and technical adviser, an expert adviser, a technical expert, a patient expert, a non-expert member of the medical technologies advisory committee and a representative of the external assessment centre.

NICE project team

Kimberley Carter
Technical Lead

Paul Dimmock
Senior Technical Analyst

Bernice Dillon
Technical Adviser

Expert advisers

Moji Awogbade
Consultant Haematologist

Gavin Cho
Consultant Haematologist

Jo Howard
Consultant Haematologist

Kelly Samuel
Patient Expert

Non-expert MTAC member

Allan Wailoo
Professor of Health Economics, School of Health and Related Research (ScHARR), University of Sheffield

External assessment centre

Iain Willits
External Assessment Centre Representative

Joyce Craig
External Assessment Centre Representative

8 Sources of evidence considered by the committee

The external assessment centre report for this assessment was prepared by Newcastle and York:

- Willits I, Cole H, Jones R, Arber M, Jenks M, Craig J and Sims A, Spectra Optia Apheresis System for automated red blood cell exchange in patients with sickle cell disease (August 2015)

Submissions from the following company:

- Terumo BCT

The following individuals gave their expert personal view on Spectra Optia by providing their expert comments on the draft scope and assessment report.

- Dr Michele Afif, ratified by the Royal College of Paediatrics and Child Health – clinical expert
- Dr Martin Besser, ratified by the Royal College of Pathologists – clinical expert
- Dr Gavin Cho, ratified by the British Society for Haematology – clinical expert
- Dr Jo Howard, ratified by the British Society for Haematology – clinical expert
- Dr Banu Kaya, ratified by the Royal College of Pathologists – clinical expert
- Dr Sally Nelson, NHS England – commissioning expert
- Dr Elizabeth Rhodes, ratified by the Royal College of Pathologists – clinical expert
- Dr Kate Ryan, ratified by the Royal College of Pathologists – clinical expert
- John James, the Sickle Cell Society – patient expert

The following individuals gave their expert personal view on Spectra Optia in writing by completing a patient questionnaire or expert adviser questionnaire provided to the committee.

- Dr Michele Afif, ratified by the Royal College of Paediatrics and Child Health – clinical expert
- Dr Moji Awogbade, ratified by the Royal College of Pathologists – clinical expert
- Dr Martin Besser, ratified by the Royal College of Pathologists – clinical expert
- Dr Gavin Cho, ratified by the British Society for Haematology – clinical expert
- Dr Jo Howard, ratified by the British Society for Haematology – clinical expert
- Dr Banu Kaya, ratified by the Royal College of Pathologists – clinical expert
- Dr Elizabeth Rhodes, ratified by the Royal College of Pathologists – clinical expert
- Dr Kate Ryan, ratified by the Royal College of Pathologists – clinical expert
- Dr Farrukh Shah, ratified by the Royal College of Pathologists – clinical expert
- Dr Sara Trompeter, ratified by the British Society for Haematology – clinical expert
- Chike Eduputa – patient expert
- John James, the Sickle Cell Society – patient expert
- Kelly Samuel – patient expert

Update information

Minor changes since publication

September 2020: We combined the first 2 recommendations into 1, and changed references to 'patients' to 'people' because sickle cell disease is a lifelong health condition. We also made some changes to make the guidance more accessible.

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