

# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Medical technology consultation document

# Spectra Optia for automated red blood cell exchange in patients with sickle cell disease

The National Institute for Health and Care Excellence (NICE) is producing guidance on using Spectra Optia for automated red blood cell exchange in patients with sickle cell disease in the NHS in England. The Medical Technologies Advisory Committee has considered the evidence submitted and the views of expert advisers.

This document has been prepared for public consultation. It summarises the evidence and views that have been considered, and sets out the draft recommendations made by the Committee. NICE invites comments from the public. This document should be read along with the evidence base (see Sources of evidence considered by the Committee).

The Advisory Committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical effectiveness and resource savings reasonable interpretations of the evidence?
- Are the provisional recommendations sound, and a suitable basis for guidance to the NHS?
- Are there any equality issues that need special consideration and are not covered in the medical technology consultation document?

**Note that this document is not NICE's final guidance on Spectra Optia for automated red blood cell exchange in patients with sickle cell disease. The recommendations in section 1 may change after consultation.** After consultation the Committee will meet again to consider the evidence, this document and comments from public consultation. After considering these comments, the Committee will prepare its final recommendations which will be the basis for NICE's guidance on the use of the technology in the NHS in England.

For further details, see the [Medical Technologies Evaluation Programme process guide](#) and [Medical Technologies Evaluation Programme methods guide](#).

Key dates:

- Closing time and date for comments: 17:00 16 November 2015

- Second Medical Technologies Advisory Committee meeting: 17 December 2015

NICE medical technologies guidance addresses specific technologies notified to NICE by sponsors. The 'case for adoption' is based on the claimed advantages of introducing the specific technology compared with current management of the condition. This case is reviewed against the evidence submitted and expert advice. If the case for adopting the technology is supported, then the technology has been found to offer advantages to patients and the NHS. The specific recommendations on individual technologies are not intended to limit use of other relevant technologies which may offer similar advantages.

## **1 Provisional recommendations**

- 1.1 The case for adopting Spectra Optia for automated red blood cell exchange in patients with sickle cell disease 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 Spectra Optia should be considered for automated red blood cell exchange in patients with sickle cell disease who need regular transfusion.
- 1.3 Cost modelling shows that using Spectra Optia is cost saving in most patients compared with manual red blood cell exchange or top-up transfusion. The savings depend on the iron overload status of the patient, and are more likely to be achieved if devices already owned by the NHS can also be used to treat sickle cell disease. Uncertainties in the cost model for adopting Spectra Optia lead to a wide range of estimated cost consequences, from a saving of £96,512 per patient per year to an additional cost of £6,046 per patient per year compared with manual exchange (see table 2a in section 5.14).
- 1.4 NICE recommends collaborative data collection on the outcomes of treatment with Spectra Optia to supplement the limited clinical

evidence on some outcomes. In particular, there is the need for long-term data on how automated and manual exchange affects iron overload status and the subsequent need for chelation therapy.

## **2 The technology**

### ***Description of the technology***

2.1 The Spectra Optia Apheresis System (Terumo) is intended for automated red blood cell depletion and exchange in adults or children with sickle cell disease who are on a transfusion regime. The system automatically replaces sickle red blood cells with healthy red blood cells. The system comprises 3 components: the apheresis machine itself, embedded software and a single-use disposable blood tubing set. Venous access for Spectra Optia is usually through a vein in the arm or large vein in the leg. The latter is a more complicated procedure that requires additional expertise and sometimes an ultrasound device. In a typical exchange procedure, the selected components of blood are separated and removed from the patient by Spectra Optia using continuous flow and centrifugation. A patented optical detection technology (known as automated interface management) monitors the composition of the blood and feeds this information to the device protocol, which can adjust appropriate pumps and valves to remove selected components. The device protocol, software and automated interface management system then control the replacement of the removed components with donor red blood cells. The device also 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 2–3 hours.

2.2 Spectra Optia has a CE mark as a Class IIb medical device. It is a blood component separator intended for use in therapeutic apheresis which may be used for red blood cell exchange, depletion and depletion/exchange procedures. 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: £45,351.60
  - Exchange/depletion software: £6700.85
- Consumables:
  - Spectra Optia exchange set: £1007.04 per 6 (£167.84 each)
  - Astotube with injection port: £218.50 per 50 (£4.37 each)
  - ACD-A anticoagulant (750 ml): £57.36 per 12 (£4.78 each)
  - Service charge: £4572 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 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 an estimated 25% of people cannot have the drug because it is not tolerated or because of contraindications. For example, pregnant and breast-feeding mothers and people planning to conceive should not take hydroxycarbamide.
- 2.7 If hydroxycarbamide cannot be used, patients may need regular elective transfusion instead. People with sickle cell disease may also need occasional emergency transfusion for acute complications. When transfusion is needed, it 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 range of factors including clinical status and the local availability of facilities and services. In general, top-up transfusions are suitable 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 associated with an accumulation of iron, which will need to be counteracted with chelation therapy (typically after 20 transfusions). It is understood that top-up transfusions are commonly used in children because they are unlikely to be iron overloaded and the small catheters used are more suitable for paediatric venous access. The larger catheters and ports used for manual and automatic exchange may be unsuitable for some children.

- 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, which may make venous access more challenging.
- 2.9 Iron overload may lead to serious long-term complications. This can be avoided through iron-neutral exchange transfusion or chelation therapy. However, chelation therapies are poorly tolerated by patients who can experience severe gastrointestinal adverse effects. 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. Patients at a high risk of stroke may be identified through the use of screening tests such as trans-cranial 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/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 43 studies including 4 studies relating to adverse events only; 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 as being 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. After excluding studies judged to be of very low quality or not of direct relevance to the decision problem, the External Assessment Centre identified 12 studies that

could potentially provide useful evidence for the evaluation. These included the 6 comparative studies identified by the company.

### **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 28.5–42%) in year 1 and 46% (range 31–48%) in year 2 compared with 33.5% across both years (range 25–42%) 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 recorded baseline patient data before the procedure, but post-procedural data were not measured. The transfused blood volume for treatment with the Cobe Spectra was higher than that with manual exchange, at 41 ml/kg (95% confidence interval [CI] 19.6–60) compared with 11.1 ml/kg (95% CI 6.6–20).
- 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 pre-defined 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 through the peripheral venous route rather than central routes more frequently ( $p<0.0001$ ). 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: 19/30 Spectra Optia and 19/21 for manual exchange, no significant difference ( $p=0.048$ )
- 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 patients 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 578–2659 ng/ml] for automated exchange and 1527 ng/ml [interquartile range 731–568 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 made within-cohort comparisons. 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 pre-specified primary end point was Spectra Optia's ability to accurately achieve targets on the fraction of a patient's original red cells remaining (fraction cells remaining, FCR), which was defined as  $0.90 \pm 0.17$  (acceptable range 0.75–1.25). The mean procedure time (and standard deviation) for the evaluable population was  $90 \pm 22$  minutes. The longest procedure time was for automated exchange in adults ( $92 \pm 24$  minutes), followed by depletion exchange procedures ( $86 \pm 16$  minutes), and the shortest procedure time was in children ( $81 \pm 16$  minutes). The mean volume of replacement blood used in all procedure types was  $1895 \pm 670$  ml; this was highest for adults ( $2118 \pm 702$  ml), lower for depletion exchange procedures ( $1562 \pm 281$  ml) and lowest in children ( $1449 \pm 260$  ml).

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 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 4–6 weeks. End points included pre- and post-procedure HbS (mean pre-procedure 47.4% [range 40.7–59.3%], mean post-procedure 25.5% [range 18.5–32.6%]), 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 <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.

3.13 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 these outcomes compared with data before erythro-exchange was started, but the reported changes were not tested for statistical significance.

3.14 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  $27.8\pm 2.4\%$ , post-procedure  $32.8\pm 1.6\%$ ) and a decrease in HbS (pre-procedure  $41.8\pm 6.1\%$ , post-procedure  $9.8\pm 2.4\%$ ) following the automated exchange protocol; the changes were not tested for statistical significance. C-RBCX procedures needed  $39.5\pm 4.6$  ml/kg packed RBC, lasted  $107.3\pm 6.7$  minutes and were done every  $37\pm 7.0$  days, leading to 7 procedures per year.

- 3.15 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 Spectra Cobe 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  $2.0\pm 1.6$  hours 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**

- 3.16 The Committee considered that the clinical evidence was limited and not of sufficient quantity or quality to evaluate all of the outcomes defined in the scope. However, it was advised that this was partly because of limitations in study methodologies, consequent upon 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 believe that Spectra Optia offers significant clinical benefits compared with manual exchange or top-up transfusion. The Committee noted that automated exchange procedures are significantly shorter and have a longer clinical benefit than manual exchange, meaning that patients need the procedure less often.

- 3.17 The Committee noted that the evidence did not show any significant differences in reducing iron overload in patients having automated exchange with Spectra Optia compared with patients having manual exchange. Nonetheless, 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.
- 3.18 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 this technique. However, during automated exchange with Spectra Optia, it is possible to replace the precise volume of sickle cells removed with the appropriate volume of packed red blood cells at a much faster rate, leading to iron neutrality.
- 3.19 The Committee noted that optimal iron management is very important in people with sickle cell disease. To avoid the serious complications of iron overload, iron chelation therapy can be used. The Committee was advised that this treatment is poorly tolerated because of side effects and that compliance is therefore low. Oral iron chelators are unpalatable and chalky and infusion pump

chelators must be administered in 3-weekly, 12-hour treatments. Side effects of chelation therapies include significant gastrointestinal symptoms. The Committee accepted expert advice that Spectra Optia is the only reliable iron-neutral transfusion therapy currently available, and that this is particularly important as chelation therapy is costly and poorly tolerated.

- 3.20 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 may depend on the availability of appropriately trained staff and that this was an important factor in the adoption of the Spectra Optia system. A patient expert added that vascular access was a source of anxiety for patients before transfusion sessions. The experts advised that access to a large central vein such as the femoral vein (often guided by ultrasound) is most commonly required with Spectra Optia. 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 required to use Spectra Optia are transferable, so staff are able to use Spectra Optia for other clinical indications.

## **4 NHS considerations**

### ***System impact***

- 4.1 Adopting the Spectra Optia is claimed to have a range of system benefits including: a reduced need for chelation therapy; shorter, less frequent exchange procedures; reduced number of staff needed; reduced emergency hospitalisations and more efficient use of donor blood. Published evidence was presented on procedure times and treatment intervals (see section 3.16) but not for the other outcomes.



- 4.2 Clinical experts informed the Committee that Spectra Optia may be operated by 1 Band 5 nurse. In larger units with more than 1 machine, 1 nurse can 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 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. It was advised by clinical experts that, during manual exchange, some donor blood may be removed from the patient and unless an extra cell separation process is performed, this donor blood is wasted.

Only sickle cells are removed by Spectra Optia so this may account for the difference, however, no studies have been conducted to investigate this.

- 4.6 The Committee noted that current levels of tariff remuneration can act as a disincentive to use this technology. The Committee was also advised by the 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 population groups were:
- Children at high risk of primary stroke, with and without iron overload (mild, moderate and severe).
  - Children having treatments to prevent complications of sickle cell disease, with and without iron overload.

- Adults having treatments 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.

5.3 In the absence of published data, 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, 36 and 48 months	90% after 12 months
Patients able to cease chelation therapy	<i>Mild iron overload:</i> 50% and 100% after 12 and 24 months <i>Moderate iron overload:</i> 5%, 15%, 30% and 50% after 12, 24, 36 and 48 months <i>Severe iron overload:</i> 5%, 15% and 30% after 24, 36 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	<i>Children and adults (complications):</i> 0.65 <i>Children (stroke):</i> 0.01	<i>Children and adults (complications):</i> 1.1 <i>Children (stroke):</i> 0.02	<i>Children (stroke):</i> 0.07
Procedure time	<i>Adults:</i> 110 minutes <i>Children:</i> 86 minutes	245 minutes	<i>Adults:</i> 300 minutes <i>Children:</i> 180 minutes
Procedures	8.5	12	13

Parameter	Spectra Optia	Manual exchange	Top-up transfusion
per year			
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.			

5.4 Parameters relating to adverse events and alloimmunisation were not included as they were considered to be similar for all modalities. The cost of stroke was taken from Cherry et al. (2012) and set as a one-off payment of £21,807 at 2.5 years into the model. The cost per hospital admission included was £1354, taken from NHS reference costs. Chelation therapy costs were calculated from British national formulary values using average body masses and taken to be £21,022 per patient per year for adults and £9954 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).

5.5 The company performed 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. Results were reported using tornado diagrams. 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.

- 5.6 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 sickle cell disease treatment over the 5-year time horizon varied from £48,093 for Spectra Optia in patients with no iron overload to £128,670 for manual exchange in patients with iron overload.
- 5.7 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**

- 5.8 Because high quality data to populate the company's model were limited, the External Assessment Centre revised the input parameters of the model to better reflect the uncertainty around published values. However, it judged that the limited data remain a key consideration when interpreting the results.
- 5.9 The company's base case assumes that 100% of the device usage and costs for Spectra Optia are attributed to treating sickle cell

disease. The External Assessment Centre considered that because the device can treat multiple indications, and because of the low incidence of sickle cell disease, it was feasible to consider that a Spectra Optia device can be shared across different indications. The External Assessment Centre calculated additional scenarios where only 50% and 30% of the device's capacity was used to treat sickle cell disease in groups of 30 and 15 patients. The company had also not included the capital costs (£52,052) and maintenance costs (£4572) for the device, which the External Assessment Centre added. The External Assessment Centre also extended the lifespan of the device from 5 to 7 years in the model.

5.10 The External Assessment Centre also noted that the cost of chelation therapy in the company's model did not include diagnostic and monitoring costs. The estimate of [REDACTED] of the chelation therapy costs 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 2–5 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).

5.11 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.

5.12 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.

5.13 At the Committee meeting, the External Assessment Centre was asked 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 receiving chelation therapy) whereas only 80% were when beginning manual exchange. The company provided no rationale for this difference so the External Assessment Centre set both starting chelation treatment rates at 90%.

5.14 Following discussion about the availability of Spectra Optia, the Committee decided that it would be most helpful if the cost modelling could include 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, it can be 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 the tables below.

**Table 2a: External Assessment Centre’s revisions to base case (automated vs manual)**

Population	No overload	Mild overload	Moderate overload	Severe overload
<b>0% capital costs for SCD</b>				
Adults	-£25,011	-£96,512	-£24,874	-£10,867
Children (2° prevention)	-£12,439	-£46,294	-£12,374	-£5,742
Children (1° prevention)	-£10,005	-£43,860	-£9,940	-£3,307
<b>50% capital costs for SCD</b>				
Adults	-£16,555	-£88,056	-£16,418	-£2,410
Children (2° prevention)	-£3,983	-£37,838	-£3,918	£2,715
Children (1° prevention)	-£1,548	-£35,404	-£1,484	£5,149
<b>100% capital costs for SCD</b>				
Adults	-£8,099	-£79,600	-£7,961	£6,046
Children (2° prevention)	£4,474	-£29,382	£4,539	£11,171
Children (1° prevention)	£6,908	-£26,947	£6,973	£13,605
Abbreviations: SCD, sickle cell disease Negative values indicate cost savings with Spectra Optia.				

**Table 2b: External Assessment Centre’s revisions to base case (automated vs top-up)**

Population	No overload	Mild overload	Moderate	Severe
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			overload	overload
<b>0% capital costs for SCD</b>				
Adults	-£77,483	-£81,493	-£9,855	(£4,152)
Children (2° prevention)	-£35,424	-£37,322	-£3,402	(£3,230)
Children (1° prevention)	-£31,681	-£33,580	£341	(£6,973)
<b>50% capital costs for SCD</b>				
Adults	-£69,027	-£73,037	-£1,399	(£12,609)
Children (2° prevention)	-£26,967	-£28,866	£5,054	(£11,687)
Children (1° prevention)	-£23,224	-£25,123	£8,797	(£15,430)
<b>100% capital costs for SCD</b>				
Adults	-£60,571	-£64,581	£7,058	(£21,065)
Children (2° prevention)	-£18,511	-£20,409	£13,511	(£20,143)
Children (1° prevention)	-£14,768	-£16,667	£17,253	(£23,886)
Abbreviations: SCD, sickle cell disease; TUT, top-up transfusion Results in brackets are considered clinically unlikely. Negative values indicate cost savings with Spectra Optia.				

5.15 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 £1484 (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 £1399 (compared with top-up transfusion in adults with moderate iron overload) per patient per year.

5.16 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 £2715 to £13605 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**

- 5.17 The Committee considered that that local providers should take into account existing available 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.
- 5.18 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.
- 5.19 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).
- 5.20 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).

- 5.21 Despite 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 reliable iron-neutral transfusion therapy available, and that this is particularly important since 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 a 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 remove the current uncertainties related to the use of the Spectra Optia device.

Peter Groves  
Vice Chair, Medical Technologies Advisory Committee  
October 2015

## **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.

#### **Professor Bruce Campbell (Chair)**

Consultant Vascular Surgeon, Royal Devon and Exeter Hospital

#### **Dr Peter Groves (Vice Chair)**

Consultant Cardiologist, Cardiff and Vale University Health Board

#### **Ms Susan Bennett**

Lay member

#### **Professor Nigel Brunskill**

Professor of Renal Medicine, University of Leicester

#### **Mr Matthew Campbell-Hill**

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**Professor Shaheen Hamdy**

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**Mr Brian Selman**

Managing Director, Selman and Company Limited

**Professor Wendy Tindale**

Scientific Director, Sheffield Teaching Hospitals NHS Foundation Trust

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**Mr John Wilkinson**

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### ***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**

Technical Analyst

#### **Bernice Dillon**

Technical Adviser

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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 sponsor:

- 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

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It has been incorporated into the NICE pathway on XXX, along with other related guidance and products. [Amend as necessary. Hyperlink to pathway from pathway name. Delete if not relevant.]

We have produced a summary of this guidance for the public [add hyperlink to the UNG page]. Tools [add hyperlink to the guidance summary page] to help you put the guidance into practice and information about the evidence it is based on are also available. [delete any wording that isn't relevant]

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