NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technology guidance

Assessment report overview

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

This assessment report overview has been prepared by the Medical Technologies Evaluation Programme team to highlight the significant findings of the External Assessment Centre (EAC) report. It includes key features of the evidence base and the cost analysis, any additional analysis carried out, and additional information, uncertainties and key issues the Committee may wish to discuss. It should be read along with the company's submission of evidence and with the EAC report. The overview forms part of the information received by the Medical Technologies Advisory Committee when it develops its recommendations on the technology.

Key issues for consideration by the Committee are described in section 6, following the summaries of the clinical and cost evidence.

This report contains information that has been accepted in confidence and will be redacted before publication. This information is highlighted in yellow. This overview also contains:

- Appendix A: Sources of evidence
- Appendix B: Comments from professional bodies
- Appendix C: Comments from patient organisations

1 The technology

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 long-term or temporary/medium-term transfusion regime.

The system comprises 3 components: the apheresis machine itself, embedded software and a single-use disposable blood tubing set. Venous access for the Spectra Optia is usually through an arm vein or large vein in the leg. The latter is a more complicated procedure that requires additional expertise, often involving a vascular radiologist.

In a typical depletion and exchange procedure, the constituent components of blood removed from the patient are separated by the Spectra Optia using continuous flow and centrifugation. A patented optical detection technology (known as automated interface management) monitors the composition of the blood components and feeds this information to the selected device protocol, which can adjust appropriate pumps and valves in real time 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 and fluid as needed. The procedure typically takes 2–3 hours.

The Spectra Optia should be operated by trained healthcare professionals. The system may be used in a specialist day-care setting and, if the patient is well enough, they may return to normal activities immediately after the procedure.

The Spectra Optia is a multifunctional system that has several applications. It was developed from a predecessor system, the Cobe Spectra, with a reduced size and weight and the option to automatically perform depletion-exchange procedures. The Spectra Optia and Cobe Spectra may be considered

clinically equivalent in terms of red cell exchange for the purpose of this evaluation.

The 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. The 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 Proposed use of the technology

2.1 Disease or condition

Sickle cell disease (SCD) is the most common serious genetic disorder in England and affects 1 in 2000 live births, or 350 babies a year (NHS Screening Programmes 2010). Although the disease can vary in severity, all patients experience acute episodes of extreme pain that can have a negative effect on quality of life. For people with more severe forms of SCD, tissue damage can lead to organ failure and stroke. Life expectancy is considerably reduced at 45–55 years.

2.2 Patient group

SCD is most common in people of African, Caribbean, Eastern-Mediterranean, Middle-Eastern or Asian family origin. In the UK, most people with SCD are of African and Caribbean family origin. In this population, between 1 in 10 and 1 in 40 people carry the sickle cell trait and between 1 in 60 and 1 in 200 have SCD (Sickle Cell Society 2009). SCD is an autosomal recessive inherited condition with different genotypes of varying clinical severity. Around 70% of people with SCD are homozygous for the recessive beta S globin and have a severe or moderately severe phenotype. Around

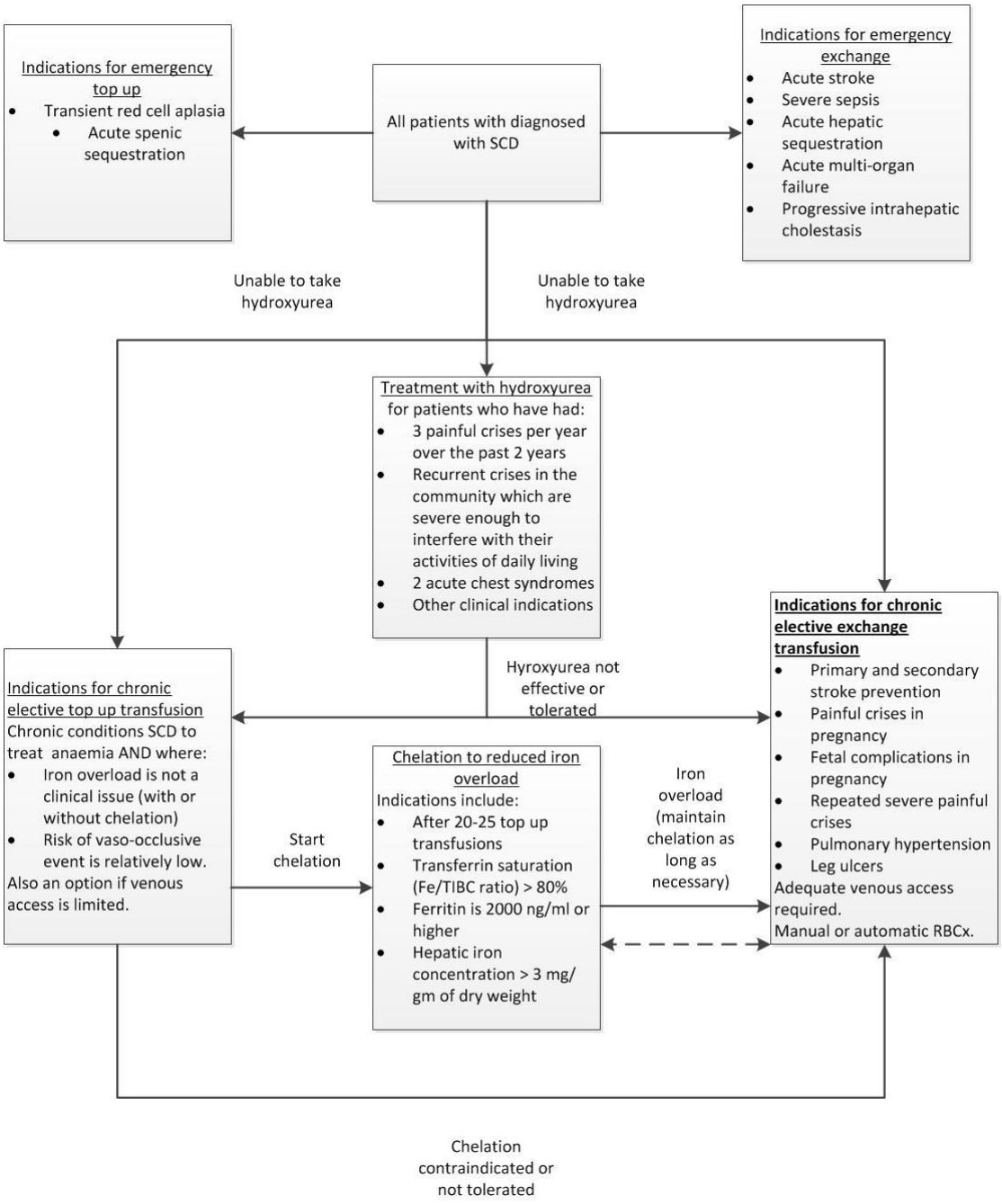
10–20% of people with SCD have long-term monthly blood transfusions or red blood cell exchange.

2.3 Current management

There are no existing NICE pathways for managing sickle cell disease patients other than for acute painful episode which is outside the scope of this evaluation.

Figure 1 summarises the current pathway for patients with SCD based on national guidelines (Howell et al. 2015, Sickle Cell Society 2008) and expert advice. For a full list of guidelines for treating SCD, please see section 2.1.2 (page 13) of the assessment report and section 3 (pages 24–25) of the submission.

Figure 1. Current patient pathway for people with SCD (figure 2.1, page 15, assessment report)



In summary, emergency treatment with top-up or exchange transfusion may be used as on occasion in patients with SCD for the indications listed. If SCD becomes more chronically symptomatic, then treatment with hydroxycarbamide (also called hydroxyurea, as in figure 1) is an option. However, approximately 25% of patients are unable to have

hydroxycarbamide because of contraindications or because they cannot tolerate it, or remain refractory to treatment. Furthermore pregnant or breastfeeding women, or people of both sexes planning to conceive, should not take hydroxycarbamide. For such patients, elective transfusions are an option.

The initial choice of transfusion therapy depends 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 unavoidable accumulation of iron, which will inevitably need chelation therapy (typically after around 20 transfusions). The alternative to top-up transfusions is red blood cell exchange transfusion. This is considered to be 'iron neutral' because the same volume of packed red blood cells is used to replace the volume of red blood cells removed from the patient's blood in an isovolaemic manner. This can be done manually or by using automated systems such as the Spectra Optia.

Services for people with SCD vary by region, with most services concentrated in major cities. Patients outside of these areas may have alternative, possibly suboptimal treatment, or need to travel for red blood cell exchange.

In its submission, the company noted that there are 57 NHS hospitals that currently have a Spectra Optia system. Of these, 27 were reported to use it for automated red blood cell exchange and most of those were reported to carry out very few procedures. The company concluded that automated red cell exchange using the Spectra Optia is currently primarily available for all patients in London and Manchester, and in Birmingham for paediatric patients only.

2.4 Proposed management with new technology

The Spectra Optia is intended for automated red blood cell depletion and exchange in adults or children with SCD who are on a long-term or temporary/medium-term transfusion regime. Introducing Spectra Optia into the patient pathway would mean only limited changes to the patient pathway, because it would be used as a direct replacement for manual red blood cell exchange (see Figure 1). The additional indications for which the Spectra Optia is designed (outside the scope of this evaluation) make it a possibility for the system to be adopted in a setting other than specialist secondary or tertiary care, such as the NHS Blood and Transplant Therapeutic Apheresis Services units. This might allow for the treatment of people with severe SCD in local centres, thus preventing the need to travel long distances.

2.5 Equality issues

No equality issues were identified relating to the use of the technology

There is currently an inequity of access to the highest standards of care for SCD because treatments are only available in certain cities in the UK.

3 Company's claimed benefits

The benefits to patients claimed by the company are:

- Automated red blood cell exchange using the Spectra Optia has a longer clinical effect than manual red blood cell exchange, meaning that patients would need the procedure only every 6–8 weeks rather than every 3–4 weeks.
- Automated red blood cell exchange with the device is faster than manual red blood cell exchange, lasting approximately 2–3 hours compared with 4–8 hours. This makes the procedure more convenient for patients, which may improve compliance.
- Having Spectra Optia may allow patients to reduce or cease iron chelation treatment because of reduced iron overloading. This medication can cause

significant side effects that may lead to poor compliance. Increased patient compliance and efficiency of automated red blood cell exchange could improve disease outcomes for patients. These improved outcomes include: reduced incidence of stroke, reduced frequency and severity of pain crises, reduced incidence of acute chest syndrome, improved outcomes following surgery, and increased BMI and growth in paediatric patients as well as improved general quality of life.

The benefits to the healthcare system claimed by the company are:

- The Spectra Optia maintains haematocrit levels which prevents iron overloading. This allows for the reduction or cessation of treatment (within 12–18 months, depending on the severity of iron overloading) with high cost, infusion-pump administered iron chelator desferrioxamine or oral chelators such as deferasirox and deferiprone.
- Reduced hospital stay and staff time needed because automated red blood cell exchange with the Spectra Optia can be done by a single trained nurse, is faster than manual exchange (2–3 hours for 6–8 units) and allows for an increased interval between treatments (every 6–8 weeks). During manual red blood cell exchange, doctors are needed to estimate haematocrit levels so that each unit of blood drawn off is replaced by the correct volume of packed red blood cells. This procedure can last for between 6 hours (3–4 units exchanged) and 2 days (8 units exchanged) depending on the patient's sickle haemoglobin levels. Manual red blood cell exchange should be repeated every 3–4 weeks.
- Reduced complications from SCD leading to reduced hospitalisations and associated treatment.
- The depletion-exchange protocol of the machine makes better use of donor blood as only the necessary component is used, allowing the remaining blood components to be used in other patients.

4 Decision problem

Table 1 Summary of the decision problem

Population	Sickle cell disease patients requiring a medium or long-term exchange transfusion regime.
Intervention	Spectra Optia Apheresis System
Comparator(s)	Manual red blood cell exchange
Outcomes	The outcome measures to consider include: Primary outcomes • Percentage of total haemoglobin that is HbS (HbS%), relative to target percentage (usually <30%) • Duration of exchange procedure • Frequency of treatment • Patient haematocrit (measure relative to prescribed target for therapy) • Iron overload and requirement for chelation therapy • Clinical outcomes including frequency of stroke, multi-organ failure, acute chest syndrome and pain crises • Quality of life • Length of hospital stay • Staff time and staff group/grade • Frequency of top-up transfusion required to treat sickle cell complications Secondary outcomes • Ease of venous access, bruising and haematoma • Device-related adverse events • Hospital admissions • Donor blood usage • BMI and growth in children
Cost analysis	Comparator(s): Manual red blood cell exchange Costs will be considered from an NHS and personal social services perspective. The time horizon for the cost analysis will be sufficiently long to reflect any differences in costs and consequences between the technologies being compared. Sensitivity analysis will be undertaken to address uncertainties in the model parameters, which will include scenarios in which different numbers and combinations of devices are needed.
Special considerations, including issues related to equality	Sickle cell disease can have a substantial and long-term adverse effect on the ability to carry out normal day-to-day activities, and as such many people with SCD will be considered to be disabled, a protected characteristic under the Equality Act, 2010. Some religious groups, for example Jehovah's Witnesses, are opposed to blood transfusions. Religion and belief is a protected characteristic under the Equality Act, 2010. The majority of people with SCD in the UK are of black African or

	Caribbean family origin. There is currently an inequity of access to the highest standards of care for SCD as treatments are only available in certain cities in the UK.

In its submission, the company proposed variations to the following domains of the decision problem:

- For the population, the company broadened the definition to include all patients needing transfusions for SCD, rather than those having exchange procedures specifically.
- For the intervention, the company included evidence for the Cobe Spectra system (the predecessor technology) as well as the Spectra Optia system. The EAC agreed that this was appropriate because in terms of efficacy the EAC considered the systems to be functionally equivalent.
- For the comparator, the company included simple or 'top-up' transfusions. The EAC did not agree this was an appropriate comparator because it is a separate procedure with different clinical indications and targets.
- For the outcomes, the company added the safety-related outcome of 'alloimmunisation' which the EAC considered was appropriate.

The cost analysis and subgroups used in the company submission were consistent with the scope.

5 The evidence

5.1 Summary of evidence of clinical benefit

The company carried out 2 separate literature reviews, identifying a total of 33 studies (see section 7.2.2 company submission page 36). However, there are inconsistencies within the company submission as 39 studies were included, with 35 studies listed in table B3 (company submission, page 40) and 4 studies relating to adverse events listed in table B10a-d (company submission, page 115).

In table B3, 5 entries each actually represented 2 studies that had been grouped into 1 primary study reference. This may account for some of the discrepancy. Only 6 of the included studies compared the Spectra Optia system, or its predecessor the Cobe Spectra system, with manual red blood cell exchange.

The EAC presented an additional literature review that identified 31 studies, including 27 of those identified by the company, as being relevant to the decision problem. It excluded 5 studies identified by the company (see table 3.1 in the assessment report) but identified 4 additional studies (a full list of the studies identified as potentially relevant by the EAC is given in table 3.2 page 37 of the assessment report). After excluding studies judged to be of very low quality or not of direct relevance to the decision problem, the EAC identified 12 studies that could potentially provide useful evidence for the evaluation. These included 6 comparative studies identified by the company (Cabibbo et al. 2005, Dedeken et al. 2014, Duclos et al. 2013, Fasano et al. 2015, Kuo et al. 2015, Woods et al. 2014) and 6 single-arm studies that were peer-reviewed and published as full papers (Quirolo et al. 2015, Bavle et al. 2014, Kalff et al. 2010, Masera et al. 2007, Sarode et al. 2011, Shrestha et al. 2015).

Comparative studies

Cabibbo et al. (2005) reported on a peer-reviewed retrospective observational study in 20 patients with sickle cell disease (SCD) who had manual or automated red blood cell exchange. In total, 206 automated exchange procedures in 13 patients were reported – 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 were reported in 7 patients. The results reported procedure time, 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.

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 the Spectra Optia was 40% (range 28.5–42%) in year 1 and 46% (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 the 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 the 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). The 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, the 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).

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 (6.6–20).

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: were simple transfusion (top-up transfusion, 20 patients), partial transfusion (details of procedure not reported, 6 patients) and automated exchange (system not specifically stated [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 this was not reported in the abstract. As well as ferritin and liver iron content, average HbS and alloimmunisation rates were reported. These were reported as rates whereas ferritin and liver iron content were reported as changes, without reference to baseline levels. The average HbS for automated exchange was 36% with an average ferritin change of −61 ng/ml/month (−161 to 17). The average HbS for partial transfusion was 34%, with an average ferritin change of 19 ng/ml/month (−42 to 106).

Kuo et al. (2015) reported on a retrospective cohort study in a published correspondence in a journal and was likely not peer reviewed. This is the only comparative study that was conducted in the UK, in 2 London centres. The aim of the study was to investigate 'whether adult SCD 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 the Spectra Optia for chronic SCD in 1 centre, and another group (n=21) who had manual exchange in another centre. 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 (median 23 years) than patients having automated exchange with the Spectra Optia (median 31 years, p=0.035), and significantly more patients having manual exchange were administered the procedure through the peripheral venous route rather than central routes (p<0.0001). The outcomes reported in the study included:

- mean pre-procedure HbS: 50% (95% CI 27% to76%) Spectra Optia compared with 55% (95% CI 16% to 72%) for manual exchange (p=0.162)
- number of patients that had less than two-thirds of procedures within the HbS target: 19/30 Spectra Optia and 19/21 for manual exchange, no significant difference
- median post-procedure haematocrit: 0.31 (0.23–0.35) for the 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 the Spectra Optia and 31 for manual exchange. Procedure time was 127 minutes for the Spectra Optia and 241 for manual exchange, and mean procedure intervals were 6.66 weeks for the 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.

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 the Spectra Optia by the company), 17 had manual exchange and 16 had both. In the second year, 13 had automated RCBX and 25 had manual exchange, but results for this year were not presented separately. Patients were actively selected for the Spectra Optia based on age and size, and could choose not to have the 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 [0.28 to 0.90] for manual exchange, p=0.27); ferritin concentrations (875 ng/ml [578–2659 ng/ml] for automated exchange and 1527 ng/ml [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

Quirolo et al. (2015) reported on a prospective multicentre study that was published in a peer-reviewed journal. The EAC highlighted this study because it made some within-cohort comparisons. Eligible and consenting patients (over 12 years age) were enrolled to have either standard exchange or automated exchange/deletion exchange with the Spectra Optia. In total, 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 the 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±0.17 (acceptable range 0.75–1.25). The mean procedure time for the evaluable population was 90±22 minutes. The longest procedure time was for automated exchange in adults (92±24 minutes), followed by depletion exchange procedures (86±16 minutes), and the shortest procedure time was in children (95±24 minutes). The mean volume of replacement blood used in all procedure types was 1895±670 ml; this was highest for adults (2118±702 ml), lower for depletion exchange procedures (1562±281 ml) and lowest in children (1449±260 ml). Secondary outcomes included the system's efficacy in achieving target haematocrit, device-related adverse effects and procedural success (procedure completion, lowering of HbS and investigator satisfaction with procedure). Procedural success outcomes were presented as yes/n) endpoints. Subgroup analysis of patients who had standard exchange (44 patients) or depletion exchange (16 patients) allowed for a comparison of the procedures, and in addition adults (40 patients) were compared with children (20 patients). Statistical methods for significance testing were not reported, and neither was the rationale for the acceptable range for the primary outcome.

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 SCD (a secondary outcome in the decision problem) who had regular exchange. The study compared the height, weight and BMI of 36 patients on long-term exchange with the patients' own height, weight and BMI before long-term exchange was started, and with 2 control groups: all patients with SCD 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 compared with before long-term exchange was started ($p \leq 0.0001$). There was also a significant increase in weight, height and BMI compared with the matched controls from the CSSCD and the entire CSSCD cohort ($p < 0.01$). Patients who had not been on regular simple transfusions before starting long-term exchange (33/36) also had a mean serum ferritin of 681 ng/ml after long-term exchange for an average duration of 63 months.

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 were had RBXC through a peripheral venous cannulae or arterio-venous fistula, generally every 4 weeks and then every 4–6 weeks. End points included pre- and post-procedure HbS (pre-procedure 47.4% [40.7–59.3%], post-procedure 25.5% [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 and maintained in patients with

normal baseline levels and reduced in those in those with slightly higher baseline levels without chelation therapy.

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 SCD 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.

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

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 SCD who had a total of 318 procedures were included for analysis. The authors reported a mean duration of 2±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.

Table 2 Characteristics of the key studies

Abbreviations used: CSSD: Cooperative Study of Sickle Cell Disease, HbS: sickle haemoglobin, IHD-RBCX: isovolaemic haemodilution RBCX, RBC: red blood cell, RBCX: red blood cell exchange, SC: sickle cell, SCD: sickle cell disease					
Study	Study design (country)	Population	Intervention versus comparator	Outcomes considered	EAC comments on study
Comparative studies					
Cabibbo et al. (2005)	Retrospective observational study Full article in peer reviewed journal Italy	20 patients (mixed age) 394 procedures	Baxter CS300+ system Haemonetics MCS+ system Cobe Spectra vs. Manual RBCX	Procedure time, RBC units used, clinical improvement, iron overload, and HbS <30% achieved	The aims of this study were not clear and results may have been reported selectively Patients that received manual RBCX were unable to have auto RBCX because of poor compliance or difficult venous access, Baseline characteristics of the two groups were very different and were not accounted for. No statistical analysis was reported.
Dedeken et al. (2014)	Retrospective 'before and after' study Conference abstract Belgium	10 older children Total number of procedures unclear (181 reported but unclear what it is referring to)	Spectra Optia (following manual RBCX) vs. Manual RBCX (before automated RBCX)	HbS%, ferritin (µg/l), duration of procedure, costs and interval between procedures	It was not possible to fully interpret the methodology used in this poorly-reported study or test the veracity of the results. The study was subject to considerable sources of bias and confounding that could not be controlled for; for instance all patients had to receive manual RBCX first before being actively selected for Spectra Optia. The reported results could not be disaggregated. The number of patients recruited was low and the number of procedures unclear.
Duclos et al. (2013)	Retrospective matched case series Full article in peer reviewed	10 older children 184 procedures	Cobe Spectra (for chronic SCD) vs. Manual RBCX	The primary outcome of the study appeared to be comparative measurement of	Limitations to this study; cohorts were treated in different centres; selection bias was minimised but not eliminated by matching and reporting bias. This study was also small. Overall this was a relatively well conducted and

Abbreviations used: CSSD: Cooperative Study of Sickle Cell Disease, HbS: sickle haemoglobin, IHD-RBCX: isovolaemic haemodilution RBCX, RBC: red blood cell, RBCX: red blood cell exchange, SC: sickle cell, SCD: sickle cell disease					
Study	Study design (country)	Population	Intervention versus comparator	Outcomes considered	EAC comments on study
	journal France			HbS% levels, although it is not clear if any outcomes were predetermined before analysis. Pre-procedure metrics were recorded but no post-procedure data were gathered. Packed RBC units used.	reported study that provides insight into the use of the Cobe Spectra system (and by extension, the Spectra Optia system) in older children. A reported relationship between HbS% levels and procedure interval was not accompanied with appropriate statistical analysis.
Fasano et al. (2015)	Retrospective observational study Conference abstract US	36 patients Minimum 6 month data collection (procedure number unknown)	Spectra Optia (confirmed by company) vs. Simple (top up) transfusion Partial exchange transfusion	Reduction of ferritin and liver iron content. Average HbS% and alloimmunisation rates were reported.	The study is so poorly reported that it was not possible to fully understand how it was conducted. The population was relevant to a subgroup specified in the scope, but was subject to a high risk of selection bias, not helped by a lack of baseline description. The method of partial exchange was not described and therefore cannot be considered as directly comparable to automated RBCX; full manual exchange was not investigated.
Kuo et al. (2015)	Retrospective observational cohort study Published in journal (probably	51 patients 401 procedures	Spectra Optia vs. Manual RBCX	Pre-procedure HbS% (“pre-RBCX HbS/SC fraction”), the proportion of sessions where the	The study was a head to head comparison of methods with a reasonably high number of enrolled patients and procedures. The study was relatively well reported and presented.

Abbreviations used: CSSD: Cooperative Study of Sickle Cell Disease, HbS: sickle haemoglobin, IHD-RBCX: isovolaemic haemodilution RBCX, RBC: red blood cell, RBCX: red blood cell exchange, SC: sickle cell, SCD: sickle cell disease					
Study	Study design (country)	Population	Intervention versus comparator	Outcomes considered	EAC comments on study
	not peer reviewed) UK			target HbS% was met (threshold at 2/3 sessions) achieving haematocrit target, resource use (packed RBC utilisation, procedure time, and procedure intervals), and adverse effects.	A weakness of the study was that it was performed in two separate hospitals. There was also the potential for reporting bias, and it is noticeable that the raw post-procedural outcome data on HbS% was not presented; instead target data was. The study was set in the UK which increases its generalisability to the decision problem, and provides some comparative evidence, which while limited, is insightful.
Woods et al. (2014)	Retrospective observational study Conference abstract US	38 patients Procedure number not reported	Spectra Optia (confirmed by company) vs. Manual RBCX	Duration and mode of transfusion therapy, achievement of HbS% targets, ferritin levels, and catheter complications.	Interpretation of the results of this study was difficult because of inadequate reporting and presentation of results. Patients were actively selected on the basis of age, so the cohorts were not directly comparable in terms of baseline characteristics. A further confounding factor was the fact that many patients received both treatments in the first year, but the data cannot be disaggregated to control for this.
Single-arm studies					
Quirolo et al. (2015)	Prospective observational study (single armed) Peer-reviewed	72 patients/ procedures (safety) 60 patients/ procedures	Spectra Optia vs. Depletion RBCX Spectra Optia (subgroup analysis)	Ability to achieve target FCR and haematocrit. Device related adverse events and procedural success.	This study had greater methodological quality than most of the studies of this system but that it was subject to potential bias in terms of patient selection and assessment bias for the subjective (secondary) outcomes. The baseline characteristics of the subgroups

Abbreviations used: CSSD: Cooperative Study of Sickle Cell Disease, HbS: sickle haemoglobin, IHD-RBCX: isovolaemic haemodilution RBCX, RBC: red blood cell, RBCX: red blood cell exchange, SC: sickle cell, SCD: sickle cell disease					
Study	Study design (country)	Population	Intervention versus comparator	Outcomes considered	EAC comments on study
	journal US	(efficacy)			receiving RBCX or depletion/exchange are not provided, so it is not possible to compare the two forms of treatment. The authors themselves concluded that further evidence is required to determine which patients may benefit most from depletion/exchange. Nevertheless, this study provides good evidence for the short-term efficacy and safety of Spectra Optia.
Bavle et al. 2014.	Retrospective observational study, matched controls Full article in peer-reviewed journal US	35 children	Cobe Spectra vs. 64 matched controls	Height, weight and BMI	This was an adequately designed and reported study, but was confounded by the use of historical controls. However, the primary outcome of interest, growth in children, was of peripheral interest only to the decision problem. The authors attempted to find two matched controls from the CSSCD dataset for every subject; although, only 1 matched control was found for 8 of the study subjects.
Kalff et al. (2010)	Retrospective case series Full article in peer reviewed journal Australia	13 patients	Cobe Spectra only	Reduction of HbS, incidence of sickle cell-related acute events, and the progression of pre-existing related end-organ damage and development of new end-organ damage	Although this study was adequately described and reported, its validity was limited by the lack of a comparator arm and the usual shortcomings associated with observational studies of this nature (in terms of confounders and bias). The authors relied on hospital and medical records which were partially complete or had been destroyed for some subjects; several patients had been transferred from another institution and had

Abbreviations used: CSSD: Cooperative Study of Sickle Cell Disease, HbS: sickle haemoglobin, IHD-RBCX: isovolaemic haemodilution RBCX, RBC: red blood cell, RBCX: red blood cell exchange, SC: sickle cell, SCD: sickle cell disease					
Study	Study design (country)	Population	Intervention versus comparator	Outcomes considered	EAC comments on study
					no baseline information. For this reason they were unable to demonstrate significant before/after comparisons for the main outcome measures.
Masera et al. (2007)	Retrospective data review Full article in peer-reviewed journal Italy	34 patients	Cobe Spectra only	Change in HbS and ferritin levels, hospital admissions and painful crises.	It was not clear how the 13 patients were selected or which treatments they received, and there were several confounding variables which were not controlled for. The study also reports on a periodic erythroexchange programme when compared to a chronic erythroexchange programme and also in combination with hydroxyurea which limits the generalisability of the results to current practice.
Sarode et al. (2011)	Retrospective observational study with historical controls Full article in peer-reviewed journal US	20 patients	Cobe Spectra isovolaemic haemodilution exchange vs. 6 historical controls (standard Cobe Spectra exchange)	Haematocrit, HbS%, packed RBC required	This study has a high potential for confounding and bias. The 6 controls selected for comparing inter-procedure intervals were historical controls and it is not clear how these controls were selected or whether they were matched to the patients in the IHD-RBCX group.
Shrestha et al. (2015)	Retrospective observational study Full article in peer reviewed journal	29 patients 318 procedures	Cobe Spectra only	Inlet speed, duration of procedure and rate of complication.	This study was designed to compare two types of venous access and that the selection of patients is not reported which opens up the potential for selection bias. The procedures for data collection were similarly not reported.

Abbreviations used: CSSD: Cooperative Study of Sickle Cell Disease, HbS: sickle haemoglobin, IHD-RBCX: isovolaemic haemodilution RBCX, RBC: red blood cell, RBCX: red blood cell exchange, SC: sickle cell, SCD: sickle cell disease					
Study	Study design (country)	Population	Intervention versus comparator	Outcomes considered	EAC comments on study
	US				

Adverse events

In the submission the company summarised 19 medical device reports for exchange procedures found in the US Food and Drug Administration's Manufacturer and User Facility Device Experience (MAUDE) database from 1 July 2010 to 23 May 2015. Additional related reports were identified in which the apheresis protocol was unknown, or faults were identified during maintenance, giving 77 in total. The company reported only 1 common device malfunction in this time period, in the return line air detector. Field safety notices (low risk) were issued worldwide by the company and these only related to the mononuclear cell collection protocols, not to any of the exchange protocols (including exchange). The EAC considered the overall device failure rate to be insignificant (77/120,000), with no reported major patient injury or death being attributed to device failure.

Catheter complications were infrequently reported in the studies and these were generally limited to cases with femoral lines in adults and large-bore double-lumen implantable port vascular access in children and adolescents. Where these occurred, the patient tended to be transitioned to a manual exchange procedure and no significant harm was reported.

EAC critical appraisal of the clinical evidence

The EAC considered that overall the company's clinical submission was well written and logically set out, but it had particular reservations about the company's proposed variations from the scope and interpretation of results.

The EAC critically appraised the methodologies of the studies identified in its own literature search and concluded that overall, the quality of evidence reported was very low. In particular:

- most of the evidence came from retrospective observational studies
- few studies were reported as full articles in peer-reviewed journals

- most were single-armed and all were subject to confounding which could not be resolved, had small sample sizes, and were subject to varying degrees of selection and reporting bias.

For this reason, the EAC focused on the 6 comparative studies and 1 single-armed prospective study that it deemed to be of higher quality. Four of the comparative studies were deemed to be of poor or very poor quality: Cabibbo et al. (2005), Dedeken et al. (2014), Fasano et al. (2015) and Woods et al. (2014). The EAC considered the studies by Duclos et al. (2013) and Kuo et al. (2015) to be of higher quality and better reported. In addition, the EAC considered that the single-armed prospective study by Quirolo (2015) provided useful supplementary data.

The EAC compared the outcomes identified in the scope with those reported in the studies, with reference to the company's claimed benefits (see table 3.11 assessment report page 109). This was done in the context of the poor methodological quality of the studies causing considerable uncertainty, even in the better reported studies. The EAC considered that there was unequivocal evidence that, compared with manual exchange, automated exchange with the Spectra Optia system was associated with a shorter duration of procedure (about half the time), a reduced frequency of treatments (2 to 3 weeks greater treatment interval), and increased use of packed RBC (approximately double for the Spectra Optia). The EAC considered that the evidence on achieving HbS and haematocrit targets and effect on iron overload was equivocal; that is, the Spectra Optia system may provide additional benefits in these terms compared with manual exchange, but this has not been adequately demonstrated. There was no comparative evidence reported on hospital admissions. There was also no usable evidence reported on staff resources, ease of venous access, quality of life and BMI growth in children. Finally, there was no evidence reported to support the claimed benefits of the Spectra Optia system on clinical and complication outcomes, such as stroke, painful crises and acute chest syndrome. The EAC concluded

that there were no significant safety concerns regarding adverse events for the Spectra Optia.

5.2 Summary of economic evidence

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

Model structure and assumptions

The company presented an economic model comparing the Spectra Optia with manual exchange. It also included top-up transfusion as a comparator in the model, although this was not specified in the decision problem. The population was considered as 12 subgroups based on a mixture of age, clinical indication and co-morbidity (degree of iron overload) to represent the heterogeneous case-mix of SCD patients having different 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, according to serum ferritin levels).
- Children having treatments to prevent complications of SCD (such as painful crises, acute chest syndrome, or priapism), refractory to hydroxycarbamide or unable to take hydroxycarbamide, with and without iron overload.
- Adults having treatments to prevent complications of SCD, refractory to hydroxycarbamide or unable to take hydroxycarbamide, with and without iron overload.

The structure of the model was a simple costing model which simulated the ‘average’ cost of chronic SCD treatment for 1 patient using 1 of 3 modalities:

automated exchange with the Spectra Optia, manual exchange, or top-up transfusion. The time horizon of the economic model was 5 years.

The EAC noted that top-up transfusion was not a comparator in the scope because it is generally used to treat anaemia and emergency crises in sickle cell patients. Top-up transfusion is not suitable as a long-term regime because it is iron-positive, and so the EAC considered it was not an appropriate comparator for automated exchange. However, several clinical experts have stated that top-up transfusion is sometimes used as a long-term therapy in hospitals where provision for sickle cell patients is very poor.

Model parameters

The parameters that were considered in the company's model are summarised in table 3.

Table 3 Clinical parameters used in the company's model

Variable	Company value	Source
Chance of iron overload	Automated exchange: 0% Manual exchange: 10%, 30% and 50% after 24, 36 and 48 months, respectively	Extrapolated from clinical evidence and UK registry data
Percentage of patients that can cease chelation therapy with automated exchange	Mild overload: 50% and 100% within 12 and 24 months Moderate overload: 5%, 15%, 30% and 50% within 12, 24, 36 and 48 months Severe overload: 0%, 5%, 15% and 30% within 12, 24 36 and 48 months.	Values are not based on specific research but are implied from the trends for reduced chelation requirements that have been seen in observational studies, and have been verified by clinical experts
Rate of hospital admissions (related to incidence of SCD complications)	Secondary prevention (adults and children): 0.65 automated exchange, 1.1 manual exchange Primary prevention (children): 0.01 automated exchange, 0.02 manual exchange, 0.07 TUT	Calculated mean (non-weighted) of estimates from small non-comparative studies
Stroke rate – secondary	Automated exchange: 0%	From a single paper of a small retrospective study in

stroke events per year	Manual exchange: 0.07 TUT: 0.07	emergency patients receiving mixed treatments. It was also unclear how value for manual exchange was derived
Adverse events	Not included in the model, considered to be similar across all treatments	Insufficient clinical evidence to inform otherwise
Alloimmunisation	Not included in the model, considered to be similar across all treatments	No indication from clinical evidence that there is any difference between automated and manual exchange.

Costs and resource use

The company's economic model incorporated a number of costs. These are summarised in table 4.

Table 4 Resources and costs used in the company's model

Variable	Company value	Source
Procedure time (minutes)	Automated exchange (adults): 110 Automated exchange (children): 86 Manual exchange (adults): 245 Manual exchange (children): 245 TUT (adults): 300 TUT (children): 180	Calculated as a mean of several comparative and single arm studies
Number of procedures required per year	Automated exchange: 8.5 Manual exchange: 12 TUT: 13	Mean values taken from clinical studies (Dedeken et al. 2014 and Kuo et al. 2015) and validated with clinical experts
Number packed RBC required (units)	Automated exchange (adults): 7 Automated exchange (children): 5 Manual exchange (adults): 4 Manual exchange (children): 4 TUT (adults): 2 TUT (children): 2	Derived from several comparative and single arm studies
Number of staff and staff grade	Automated exchange: 1 grade 5	Clinical expert advice

	Manual exchange: 1.5 'highly qualified' TUT: 0.5 grade 5	
Cost of stroke	£21807 one-off payment placed at 2.5 years in model	Cherry et al. 2012
Cost of hospital admission	£1354 (range £423–3832)	NHS reference cost data
Chelation therapy costs (per year)	Adults: £21022 Children: £9954	BNF unit prices and estimated body masses
Consumables	£167.84 Spectra Optia exchange set All other consumables used by all modalities	Company list price
Packed RBC (unit)	£120	NHSBT reference price

Sensitivity analysis

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, RBC units, procedure duration and frequency, and 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 conducted 4 scenario sensitivity analyses: use of depletion exchange protocol with the Spectra Optia, resulting in a reduction in the number of packed RBC 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.

Results

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 (see table 5 for all subgroups). The

absolute costs of SCD treatment over the 5-year time horizon varied from £48,093 for the Spectra Optia in patients with no iron overload to £128,670 for manual exchange in patients with iron overload. For patients having automated exchange with the Spectra Optia system, absolute treatment costs increased according to level of overload, regardless of patient characteristics or indication. However, the degree of initial overload (mild to severe) did not affect the results for patients having manual exchange or top-up transfusions, because in the model these patients did not alter their iron overload status and the regimen used for chelation was not related to severity of overload.

In the model the cost of chelation is a substantial component of the overall costs, particularly in patients having top-up transfusions where chelation accounts for 70% of adult costs (90% of these patients are assumed to need chelation after 1 year). For patients having manual exchange, staffing costs are higher than for alternative treatments. For patients having automated exchange with the Spectra Optia, the need for packed RBC is the largest cost component (almost 70% of the total cost).

The cost of hospital admissions was lowest in patients having automated exchange with the Spectra Optia, but because the differences were under £3000 this was not a major cost driver. Similarly, including strokes across the treatment modalities had little effect on the cost (at most about £1500 over 5 years) due to the low absolute incidence rates used for all modalities. As expected, the cost of chelation was not related to severity in patients having manual exchange or top-up transfusions, but increased according to severity in patients having automated exchange with the Spectra Optia. The chelation costs were a higher proportion of total costs in patients having top-up transfusions than other modalities; for example, in adults with mild iron overload having top-up transfusions, chelation represented 74% of costs compared with 61% for manual exchange and 37% for automated exchange with the Spectra Optia.

Table 5 Results of company de novo analysis –5-year per-patient costs for treatment options (negative values indicate a cost saving)

Population	Option	No overload	Mild overload	Moderate overload	Severe overload
Adults	Auto vs manual	−£18,797.71	−£52,516.78	−£8,890.58	−£360.27
	Auto vs TUT	−£51,881.94	−£42,741.78	£884.42	£9,414.73
Paediatric secondary prevention	Auto vs manual	−£20,020.63	−£35,986.75	−£15,329.57	−£11,290.44
	Auto vs TUT	−£23,302.11	−£18,974.21	£1,682.97	£5,722.10
Paediatric primary prevention	Auto vs manual	−£17,586.39	−£33,552.51	−£12,895.33	−£8,856.19
	Auto vs TUT	−£19,559.44	−£15,231.54	£5,425.64	£9,464.78

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

EAC revisions to the company's model

Because there was limited good quality data available to populate the company's model, the EAC revised the input parameters of the model to better reflect the uncertainty around published values. However, the data limitations remain a key issue when interpreting the results.

In the company's base case, 100% of the device usage and costs are attributed to use in treating SCD. However, it is estimated that based on 30 patients having an average of 8.5 automated exchange procedures per year, each taking around 2 hours, the device will be used to treat SCD for 510 hours per year. Based on a 37.5-hour week for 50 weeks per year, there are 1,875 working hours per year. This means that, in practise, only around 30%

of the Spectra Optia's capacity will be used to treat SCD. In reality, this figure will likely be lower because of the time needed to move equipment and block sessions. As such, it is estimated that based on 30 patients having automated exchange per year, 50% of the Spectra Optia's capacity will be utilised. A similar calculation suggests that if 15 patients have automated exchange per year, 70% of the system's capacity will be left unutilised. Because of the system's multi-functionality, it could be used in other departments when not being used in its capacity to treat SCD. This has been considered in the EAC's modelling scenario.

The company's base case did not include the capital and maintenance costs of the Spectra Optia. The EAC has updated the analysis to include the cost of both purchasing and maintaining the device. These costs were obtained from the company submission and spread over an estimated 7-year lifespan of the device. As the model's time horizon was limited to 5 years, the residual value of the device in years 6 and 7 was discounted (at a rate of 3.5% per year) and applied.

In order to determine the cost per patient, the cost of the device was divided by the number of patients using the device each year. This was estimated to be between 15 and 30 patients per year. The capital costs of the device are incurred upfront and are therefore not discounted. The maintenance costs have been discounted at a rate of 3.5% per year. The capital costs and maintenance costs per patient were £589 and £356 for 15 patients and £707 and £427 for 30 patients respectively.

In the company's base case the cost of chelation therapy only included medication costs, but the EAC noted that this therapy would also incur diagnostic and monitoring costs. In addition, there are potential costs from poorly controlled iron management. The EAC was unable to cost these fully but information provided in confidence showed that the cost of diagnostics for chelation therapy was [redacted] of the cost of drug therapy.

The company had assumed that 90% of patients would have chelation therapy after top-up transfusion in years 2–5 of the model. These patients entered the model with no iron overload. The EAC revised this value to 75% based on 250 of 332 patients in the Haemoglobinopathy Registry Report having regular chelation therapy (Foster 2014).

The company's base case assumed that the amount of packed RBC used in manual exchange in children was the same as that used in manual exchange in adults. The EAC judged that it was unlikely that children would need the same number of packed RBC units and reduced this amount from 4 units to 3. Following this change, the EAC also decreased the procedure time for manual exchange in children to 85% of the total adult time (245 minutes to 208 minutes). This assumption was based on exchange duration time provided by Quirolo et al. (2015) and reports of issues of venous access, pressures and flow rates that may limit total procedure time.

The company's model assumed that 1.5 staff members per patient were present during manual exchange. Based on expert opinion, the EAC judged that only 1 staff member per patient is likely to be needed for manual exchange. For automated exchange, clinical expert opinion varied; 1 expert suggested that multiple patients could be supervised by 1 staff member during the procedure (see EAC correspondence log). To be conservative, the EAC has assumed that 1 staff member per patient is needed for both manual and automated exchange (although this may underestimate the benefits of automated exchange).

Table 6 EAC revisions to the company's model

Parameter	Company base-case	EAC input value	Source
Cost of purchasing a Spectra Optia device	Not included	£52,052	Company submission (cost of device and software)
Cost of Spectra Optia maintenance per year	Not included	£4,572	Company submission (service charge)
Lifespan of device (years)	5 years	7 years	Based on information provided in confidence

Number of patients using device per year	(100%)	15-30 patients	Based on information provided in confidence
Cost of chelation therapy (adults and children)	£21,022	£34,520	Based on information provided in confidence
	£9,954	£16,345	
Proportion of patients receiving chelation therapy in years 2–5 of TUT	90%	75%	Haemoglobinopathy Registry Report
Packed RBC units required for children undergoing manual exchange	4	3	EAC
Manual exchange procedure time in children	254 minutes	208 minutes	Based on Quirolo et al. 2015
Number of staff per patient manual exchange	1.5	1	Expert opinion (see EAC Correspondence Log)

The results of the company's model using the EAC's assumptions and inputs are presented in table 7.

Table 7 Results of EAC's cost analysis based on 30 patients per year (the figures in brackets assume only 50% of the device costs are incurred by these patients)

Population	Option	No overload	Mild overload	Moderate overload	Severe overload
Adults	Optia	£65,006 (£56,550)	£111,083 (£102,627)	£182,721 (£174,265)	£196,729 (£188,272)
	Manual	£73,105	£174,551	£174,551	£174,551
	TUT	£125,577	£175,663	£175,663	£175,663
Paediatric secondary prevention	Optia	£54,933 (£46,477)	£76,750 (£68,294)	£110,670 (£102,214)	£117,303 (£108,846)
	Manual	£50,459	£98,494	£98,494	£98,494
	TUT	£73,444	£97,159	£97,159	£97,159
Paediatric	Optia	£51,450 (£42,994)	£73,267 (£64,811)	£107,188 (£98,731)	£113,820 (£105,364)

primary prevention	Manual	£44,542	£92,577	£92,577	£92,577
	TUT	£66,218	£89,934	£89,934	£89,934
The main results are based on 30 patients having automated exchange with the Spectra Optia per year, and each patient incurring the full cost. The results provided in brackets are based on 30 patients having automated exchange with the Spectra Optia per year, but with 50% of the device costs being incurred by patients within the scope of this assessment and the rest being occurred by other patients.					

In tables 8 and 9 the incremental results of the cost analysis are presented based on 30 patients having automated exchange with the Spectra Optia per year at 100% and 50% use of the device's capacity. A negative incremental cost (grey shading) indicates that automated exchange is cost saving over the alternative.

Table 8 Incremental results of model with EAC revisions based on 30 patients per year using 100% of device capacity

Population	Option	No overload	Mild overload	Moderate overload	Severe overload
Adults	Auto vs manual	−£8,099	−£63,468	£8,170	£22,177
	Auto vs TUT	−£60,571	−£64,581	£7,058	£21,065
Paediatric secondary prevention	Auto vs manual	£4,474	−£21,744	£12,177	£18,809
	Auto vs TUT	−£18,511	−£20,409	£13,511	£20,143
Paediatric primary prevention	Auto vs manual	£6,908	−£19,309	£14,611	£21,243
	Auto vs TUT	−£14,768	−£16,667	£17,253	£23,886

Table 9 Incremental results of model with EAC revisions based on 30 patients per year using 50% of device capacity

Population	Option	No overload	Mild overload	Moderate overload	Severe overload
Adults	Auto vs manual	−£16,555	−£71,925	−£287	£13,721
	Auto vs TUT	−£69,027	−£73,037	−£1,399	£12,609

Paediatric secondary prevention	Auto vs manual	−£3,983	−£30,200	£3,720	£10,353
	Auto vs TUT	−£26,967	−£28,866	£5,054	£11,687
Paediatric primary prevention	Auto vs manual	−£1,548	−£27,766	£6,154	£12,787
	Auto vs TUT	−£23,224	−£25,123	£8,797	£15,430

Table 10 presents the results based on 15 patients having automated exchange with the Spectra Optia per year.

Table 10 Results of EAC's cost analysis (15 patients a year)

Population	Option	No overload	Mild overload	Moderate overload	Severe overload
Adults	Optia	£81,919 (£58,241)	£127,996 (£104,318)	£199,634 (£175,956)	£213,641 (£189,964)
	Manual	£73,105	£174,551	£174,551	£174,551
	TUT	£125,577	£175,663	£175,663	£175,663
Paediatric secondary prevention	Optia	£71,846 (£48,168)	£93,663 (£69,985)	£127,583 (£103,905)	£134,216 (£110,538)
	Manual	£50,459	£98,494	£98,494	£98,494
	TUT	£73,444	£97,159	£97,159	£97,159
Paediatric primary prevention	Optia	£68,363 (£44,685)	£90,180 (£66,502)	£124,100 (£100,423)	£130,733 (£107,055)
	Manual	£44,542	£92,577	£92,577	£92,577
	TUT	£66,218	£89,934	£89,934	£89,934

The main results are based on 15 patients having automated exchange with the Spectra Optia per year, and each patient incurring the full cost.

The results provided in brackets are based on 15 patients having automated exchange with the Spectra Optia per year, but with 30% of the device costs being incurred by patients within the scope of this assessment and the rest being occurred by other patients.

In tables 11 and 12 the incremental results of the cost analysis are presented based on 15 patients having automated exchange with the Spectra Optia per

year at 100% and 50% use of the device's capacity. A negative incremental cost (grey shading) indicates that automated exchange is cost saving over the alternative.

Table 11. Incremental results of EAC's cost analysis (15 patients per year, 100% of device capacity)

Population	Option	No overload	Mild overload	Moderate overload	Severe overload
Adults	Auto vs manual	£8,814	−£46,556	£25,083	£39,090
	Auto vs TUT	−£43,658	−£47,668	£23,970	£37,978
Paediatric secondary prevention	Auto vs manual	£21,386	−£4,831	£29,089	£35,722
	Auto vs TUT	−£1,598	−£3,497	£30,424	£37,056
Paediatric primary prevention	Auto vs manual	£23,821	−£2,397	£31,524	£38,156
	Auto vs TUT	£2,145	£246	£34,166	£40,799

Table 12 Incremental results of EAC's cost analysis (15 patients per year, 50% of device capacity)

Population	Option	No overload	Mild overload	Moderate overload	Severe overload
Adults	Auto vs manual	−£14,864	−£70,233	£1,405	£15,412
	Auto vs TUT	−£67,336	−£71,346	£292	£14,300
Paediatric secondary prevention	Auto vs manual	−£2,291	−£28,509	£5,412	£12,044
	Auto vs TUT	−£25,276	−£27,175	£6,746	£13,378
Paediatric primary prevention	Auto vs manual	£143	−£26,074	£7,846	£14,478
	Auto vs TUT	−£21,533	−£23,432	£10,488	£17,121

Results from the economic modelling with the EAC revisions show that:

- For 30 patients having automated exchange with the Spectra Optia per year at 100% use of the device's capacity, the 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 with the Spectra Optia per year at 50% use of the device's capacity, the 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 with the Spectra Optia per year at 100% use of the device's capacity, the Spectra Optia is cost saving compared with manual exchange in all patients with mild iron overload.

- For 15 patients having automated exchange with the Spectra Optia per year at 50% use of the device's capacity, the 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 in secondary prevention only.

6 Ongoing research

The EAC and the company did not report any ongoing studies. Currently, there is a lack of good quality clinical evidence to support the clinical benefit of the Spectra Optia system compared with equivalent exchange methods. Although a suitably powered, prospective trial of adequate duration might answer some of the existing uncertainties concerning this technology, the EAC considers that it is highly unlikely that this type of research will be done in the future. This is because there is a lack of clinical equipoise; that is, although there is equivocal evidence that Spectra Optia is at least as clinically effective as manual red blood cell exchange, it has several patient advantages to the extent that it would be unethical for any centre currently using the system to randomise or otherwise switch patients to manual exchange. The

expert advisors to the EAC were unanimous on this issue (see EAC correspondence log).

7 Issues for consideration by the Committee

Clinical evidence

- The clinical evidence for the Spectra Optia is of poor quality and any conclusions drawn may underestimate the clinical potential of the device. It is important to note that there are legitimate reasons for this weak evidence base, including low disease prevalence and a lack of clinical equipoise. Clinical experts contacted by the EAC unanimously state that the Spectra Optia has additional clinical benefits that are not captured by the evidence.
- Automated red blood cell exchange simplifies the process of manual exchange, and in theory should allow different centres to provide more similar levels of care and homogenise sickle cell disease services across the UK.

Cost evidence

- The results of the EAC modelling indicate that the Spectra Optia is cost saving for people with mild or no iron overload, but cost incurring in most scenarios for people with moderate or severe iron overload.
- The automated red blood cell exchange process requires much less input from staff, allowing them to do other activities. A lower grade staff member can operate the device and would potentially need less training than for manual exchange. This could lead to considerable cost savings that may not have been fully realised in the cost modelling because of the limited sources of information available.
- The multi-functionality of the Spectra Optia and its existence in some hospitals may have further cost-saving implications. Although the EAC included the device's capital costs in the revised model, some centres already have access to the Spectra Optia and may be able to share its use across different patient groups, including people with sickle cell disease.

8 Authors

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NICE Medical Technologies Evaluation Programme

September 2015

Appendix A: Sources of evidence considered in the preparation of the overview

Details of assessment report:

9 Willits I, Cole H, Jones R, et al. Spectra Optia Apheresis System for automated red blood cell exchange in patients with sickle cell. August 2015.

Submissions from the following companies:

10 Terumo

Related NICE guidance

Sickle cell acute painful episode: Management of an acute painful sickle cell episode in hospital. NICE clinical guideline 143 (2012). Available from www.nice.org.uk/guidance/CG143

Antenatal care. NICE clinical guideline 62 (2008). Available from www.nice.org.uk/guidance/CG62

References

Bavle A, Raj A, Kong M, Bertolone S. Impact of long-term erythrocytapheresis on growth and peak height velocity of children with SCD. Pediatr Blood Cancer. 2014 Nov;61(11):2024-30.

Cabibbo S, Fidone C, Garozzo G, Antolino A, Manenti GO, Bennardello F, et al. Chronic red blood cell exchange to prevent clinical complications in SCD. Transfus Apheresis Sci. 2005 Jun;32(3):315-21.

Dedeken L, Le PQ, Rozen L, El Kenz H, Huybrechts S, Devalck C, et al. Clinical benefit and costs' evaluation of erythocytapheresis compared to manual exchange transfusion for children with SCD: A single center experience. Blood. 2014 06 Dec;124 (21).

Duclos C, Merlin E, Paillard C, Thuret I, Demeocq F, Michel G, et al. Long-term red blood cell exchange in children with SCD: manual or automatic? Transfus Apheresis Sci. 2013 Apr;48(2):219-22.

Fasano R, Kaushal M, Leong T, Sagiv E, Meier E, Luban N. Efficacy of red cell exchange, partial manual exchange, and simple transfusion, concurrently with iron chelation therapy, in reducing iron overload in chronically transfused sickle cell patients. Pediatr Blood Cancer. 2015 Jun;62:23-.

Foster M. Sickle Cell Reports. National Haemoglobinopathy Registry: Report 2013/2014; 2014

Howell C, Douglas K, Cho G, El-Ghariani K, Taylor P, Potok D, et al. Guideline on the clinical use of apheresis procedures for the treatment of patients and collection of cellular therapy products. Transfusion medicine (Oxford, England). 2015;25(2):57

Kalff A, Dowsing C, Grigg A. The impact of a regular erythrocytapheresis programme on the acute and chronic complications of SCD in adults. British Journal of Haematology. 2010 Jun;149(5):768-74.

Kuo KH, Ward R, Kaya B, Howard J, Telfer P. A comparison of chronic manual and automated red blood cell exchange transfusion in SCD patients. British Journal of Haematology. 2015 Jan 27.

Masera N, Tavecchia L, Pozzi L, Riva F, Vimercati C, Calabria M, et al. Periodic erythroexchange is an effective strategy for high risk paediatric patients with sickle-cell disease. Transfus Apheresis Sci. 2007 Dec;37(3):241-7.

NHS Screening Programmes (2010) Sickle cell disease in childhood

Quirolo K, Bertolone S, Hassell K, Howard T, King KE, Rhodes DK, et al. The evaluation of a new apheresis device for automated red blood cell

exchange procedures in patients with SCD. Transfusion. 2015 01 Apr;55(4):775-81.

Sarode R, Matevosyan K, Rogers ZR, Burner JD, Rutherford C. Advantages of isovolemic hemodilution-red cell exchange therapy to prevent recurrent stroke in sickle cell anemia patients. Journal of Clinical Apheresis. 2011;26(4):200-7.

Shrestha A, Jawa Z, Koch KL, Rankin AB, Xiang Q, Padmanabhan A, et al. Use of a dual lumen port for automated red cell exchange in adults with SCD. J Clin Apher. 2015 Mar 19.

Sickle Cell Society awareness month (2009)

SCS. Standards for the Clinical Care of Adults with Sickle Cell Disease in the UK. Sickle Cell Society; 2008.

TAS. Therapeutic Apheresis Services. 2015 [cited 2015 12th August]; Available from: http://hospital.blood.co.uk/patient-services/therapeutic-apheresis-services/

Woods D, Hayashi RJ, Fields ME, Hulbert ML. Chronic manual exchange transfusions compared with erythrocytapheresis in children and teens with SCD. Blood. 2014 06 Dec;124 (21).

Appendix B: Comments from professional bodies

Expert advice was sought from experts who have been nominated or ratified by their Specialist Society, Royal College or Professional Body. The advice received is their individual opinion and does not represent the view of the society.

Dr Michele Afif
Consultant Paediatrician and Paediatric Lead for Haemoglobinopathy, the Royal College of Paediatrics and Child Health

Dr Moji Awogbade
Consultant Haematologist, the Royal College of Pathologists

Dr Martin Besser
Consultant Haematologist, the Royal College of Pathologists

Dr Gavin Cho
Consultant Haematologist, the British Society for Haematology

Dr Jo Howard
Consultant Haematologist, the British Society for Haematology

Dr Banu Kaya
Consultant Haematologist, the Royal College of Pathologists

Dr Elizabeth Rhodes
Consultant Haematologist, the Royal College of Pathologists

Dr Kate Ryan
Consultant Haematologist, the Royal College of Pathologists

Dr Farrukh Shah
Consultant Haematologist, the Royal College of Pathologists

Dr Sara Trompeter
Consultant Paediatric Haematologist, the British Society for Haematology

Personal experience with technology

All but two of the experts have had direct involvement with the device. The two experts that have not had direct involvement with the device have referred patients for its use and would like to use the technology in future. Four have been involved in research and audits on its use.

The technology

Nine experts stated that this device was a significant modification on current methods of treatment with the one claiming that it is entirely novel.

The experts stated that the most appropriate use of this technology was for the treatment of sickle cell patients experiencing acute complications (acute chest syndrome, stroke, multiorgan failure), prior to any required surgery and in long term transfusion regimes.

Comparators

Seven experts agreed that top-up transfusion, and subsequent iron chelation therapy, is an appropriate comparator. Eight experts also listed manual red cell exchange as a comparator. One expert stated that other apheresis machines should be used as a comparator but did not specify a particular device. Another expert stated that the Haemonetics MCS+ and Freesenius Kabi are competing products.

Patient benefits

All experts agreed that the likely benefits for patients being treated with Spectra Optia were improved control of HbS levels; decreased time spent in hospital and increased treatment intervals, and reduction in iron overloading and iron chelation therapy. One expert stated that the device can be life-saving in an emergency situation and noted that when used in secondary or primary prevention of complications can lead to decreased morbidity. One expert noted that Spectra Optia was highly tolerable for patients. All experts

agreed that these benefits are likely to be realised in practice. The experts predicted that the obstacles to this include: upfront cost/availability of the device, venous access and availability of trained staff.

The experts advised that these benefits could be measured in a number of ways, such as, measuring HbS levels over the course of treatment, regular assessment of iron overloading (via ferritin levels and liver iron concentration) and the need for chelation therapy, length of time spent in hospital and patient quality of life questionnaires.

Five experts stated that there is good evidence collected locally by centres to support these benefits but that there are no RCTs. One expert stated that the evidence to support these benefits is in an early stage or is anecdotal. One expert stated that there was not much evidence available, 2 experts stated the quality of the evidence is moderate, another expert felt that the available evidence is of good quality.

Three experts stated that the use of Spectra Optia offered significant improvements in quality of life for patients due to the more convenient nature of treatment compared with top-up transfusions and manual red cell exchange. One of these experts also stated that the device could reduce symptoms in patients as HbS levels are better controlled. Another expert stated that the device is safe for use in smaller and paediatric patients.

Healthcare system benefits

Seven experts state that the use of Spectra Optia is likely to lead to cost savings for the NHS. The experts state that these benefits are likely to come from reduced lengths of stay in hospitals and day unit (8 experts), reduction or cessation of chelation therapy (6 experts) and reduced need for treatment of symptoms and complications (7 experts). All experts feel that these benefits are likely to be realised in practice.

The experts state that an economic evaluation of the length of time spent in hospital, decrease in chelation therapy and reduced rates of admissions due to complications could be used to measure this. Two experts stated that the evidence to support this is of good quality, five were unsure and three experts mentioned anecdotal evidence from individual centres.

Facilities training and functioning

Five experts stated that use of the device requires specialist training and staffing. Two experts stated that a vascular access team may be required. Experts that have used the device say that it is highly reliable.

Costs

Four experts state that the initial cost of the device, and the associated training required, is high. However, 4 experts state that there are significant cost savings to be had from the reduction in requirements for chelation therapy and in reduced time spent in hospital. One expert noted that there may be additional costs from the increased blood units required and another expert noted that radiology may be required to insert a femoral line.

General advice

Five experts stated that there is a high inequity in services for patients with SCD in different areas of the UK and that the widespread use of this device could help to address that.

All experts agree that NICE guidance on this topic would be very useful.

Appendix C: Comments from patient organisations

Advice and information was sought from patient and carer organisations. The following patient and carer organisations responded:

The Sickle Cell Society

Anecdotal evidence from clinicians and members of the Sickle Cell Society suggests benefits in both the quality and convenience of treatment with Spectra Optia. The Society cites reduced frequency of treatment and shorter treatment durations as factors which could improve patient quality of life, particularly in children. The society felt that this treatment may be more acceptable to patients, particularly those who are difficult to manage and non-compliant with current treatment regimes. The potential for the elimination of chelation therapy is also of great benefit to patients as the side effects of treatment can have a significant impact on the life of the patient.

The Society acknowledges that there is also evidence of improved treatment outcomes for patients with Spectra Optia, including a reduced risk of stroke and decreased frequency of pain crises.

The Society is not aware of any reports of side effects with the use of Spectra Optia but states that transparency is important in this regard. The Society states that one of the major problems with Spectra Optia is that it is only available in a select few specialist centres meaning that patients have to travel long distances to receive the best treatment.

The Society also notes that it is important that non-specialist clinicians are aware that the device can be used in children as well as adults. An improvement in the awareness in treatment regimens for sickle cell disease is also a requirement; the Society feels that any guidance produced on this topic would be very useful.