External Assessment Centre report

The purpose of the External Assessment Centre (EAC) report is to review and critically evaluate the company's clinical and economic evidence and may include additional analysis of the submitted evidence or new clinical and/or economic evidence.

Title: Spectra Optia Apheresis System for automated red blood cell exchange in patients with sickle cell disease

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Date completed: 25/08/2015 (post-company fact check amendments)

Declared interests of the authors

None

Acknowledgements

Colleagues from Newcastle and York EAC supported the report authors with the following tasks:

Derek Bousfield provided the technical comparison between Spectra Optia and Cobe Spectra from company website information (Appendix A).

Matthew Dunn provided cross check of tabulated results in the company evidence submission against the original published studies.

Kim Keltie provided independent quality assurance of the company's economic model.

Rider on responsibility for report

The views expressed in this report are those of the authors and not those of NICE. Any errors are the responsibility of the authors.

Contents

1 Summary

In this assessment report, “company” refers to Terumo Medical Corporation who were represented in the clinical and economic submissions by CEDAR Healthcare Technology Research Centre. “EAC” refers to the Newcastle and York External Assessment Centre, the authors of this assessment report. “Clinical experts” refers to specialists in SCD and RBCx who were approved by NICE and advised the EAC in the preparation of this report. “Clinical advisors” refers to specialists from whom the company received advice during the preparation of their submission.

Scope of the company submission

The scope described by the company was mismatched to that of the decision problem [1] in several of the domains. For the population, the company broadened the definition to include all patients requiring transfusions for sickle cell disease, rather than those receiving 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 systems are functionally equivalent. For the comparator, the company included simple or ‘top up’ transfusions as a comparator. The EAC did not consider this was an appropriate comparator as it is a different procedure with different 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 were consistent with the scope.

Summary of clinical evidence submitted by the company

The company performed an adequate literature search and sift using inclusion and exclusion criteria consistent with the original scope. Additional studies were found by searching proceedings of annual conferences known to be relevant. Studies were also included that compared automated red blood cell exchange (RBCx) with top up transfusions; the searching methodology of these studies was not described causing the potential for bias. In total, 30 studies were reported in the company submission.

Six studies compared the Spectra Optia system, or its predecessor the Cobe Spectra system (claimed as efficaciously equivalent), with manual RBCx [2-7]. These were all retrospective observational studies which did not use an experimental comparative design; three used historical controls [2, 5, 7], one was a before and after study [3] and two were between centres studies [4, 6]. Only two of the studies were peer reviewed [2, 4], one was a published letter [6] and three were reported as conference abstracts [3, 5, 7].

Of the other 24 studies, 14 were single armed studies that reported absolute or 'before and after data', with six published as full peer-reviewed studies [8-13] and 8 as conference abstracts. Two were single armed studies on manual exchange, both published as conference abstracts. Three studies compared technical aspects of the Spectra Optia and Cobe Spectra system, and four studies compared automated RBCx with top up transfusions. One study was in pregnant women.

The company critically appraised the identified studies fairly and presented the results in tabular form. However, although the company described many of the limitations of individual studies, it did not fully describe how this uncertainty might affect confidence in the overall results. The company was correct in not attempting data synthesis due to the heterogeneous nature of the studies; instead it presented the results of each study in tabular format and matched individual study results against the outcomes and benefits listed in the scope [14]. The company combined results from single armed and comparative studies in its interpretation, which led to an imbalance of data on the intervention (automated RBCx) compared with the comparator.

The company interpreted the clinical evidence as demonstrating that Spectra Optia resulted in shorter procedure times, longer intervals between procedures and increased use of packed red blood cells. In addition, it reported that automatic RBCx was superior to manual RBCx at reducing ferritin levels, and that there was general equivalence with regard to the physiological parameters of HbS and haematocrit.

Summary critique of clinical evidence submitted by the company

The EAC was unable to fully replicate the company's literature search and performed its own, broader, search. This identified four additional studies [15-18], but these were conference abstracts that did not help in answering the decision problem. Thus the EAC is confident that all relevant studies were included.

The majority of the evidence was from retrospective observational studies, which were subject to potential confounding, selection bias and reporting bias. Most of the studies were single-armed and not designed to directly compare the intervention with the comparator. The heterogeneous nature of the studies did not allow for meaningful data synthesis. The EAC noted that the quality of reporting was often poor. Only a minority of the studies were reported as full articles in peer-reviewed journals [2, 4, 8-12, 19, 20].

The EAC focussed on results from the six comparative studies with manual RBCx [2-7] and the single armed studies of the Spectra Optia system [11] and

Cobe Spectra systems [8-10, 12, 13] that were peer-reviewed. The EAC considered that there was unequivocal evidence that, compared with manual RBCx, 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 Spectra Optia). The EAC considered that the evidence on achieving HbS (%), haematocrit targets, and effect on iron overload was equivocal. There was no comparative evidence reported on hospital admissions. There was no meaningful comparative 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 comparative benefit of the Spectra Optia system on clinical and complication outcomes, such as stroke, painful crises, and acute chest syndrome, and no studies provided results according to iron overload status.

Summary of economic evidence submitted by the company

The company identified seven studies using the Cobe Spectra or Spectra Optia systems that included economic information [3, 9, 10, 12, 21-23]. However, these studies were deemed by the company to be unhelpful because they were poorly reported and were not robust; therefore they were not considered further. The EAC agreed with this assessment.

The company developed a basic economic model that aimed to estimate the overall procedural and clinical costs associated with 5 years management of chronic, severe SCD using automated RBCx (the Spectra Optia system), manual RBCx, or simple ‘top up’ transfusions. The model described 12 scenarios with starting populations with different baseline characteristics and iron overload severities. This meant that an overall ‘average’ cost of management per person with SCD or overall budgetary impact could not be calculated.

The company reported that, in the base case, Spectra Optia was always cost saving compared to manual RBCx, with savings ranging from £360 to £52,516 per patient over 5 years. In half of the scenarios (6/12), top up transfusion was cost saving compared with RBCx. Spectra Optia was associated with a greater requirement for packed RBC units than its comparators. For top up transfusions, chelation costs were the most important costs. Manual RBCx was associated with both relatively high procedural costs (through staffing requirements) and chelation costs, and therefore was therefore the most expensive option. The company conducted extensive univariate, threshold and sensitivity analysis on each scenario presented in the model. These were mainly based on adjusting healthcare resources and unit costs, and in general the results of the analyses favoured Spectra Optia.

Summary critique of economic evidence submitted by the company

The EAC considered that the *de novo* model had several shortcomings. The EAC had several major concerns. Firstly, the model incorporated estimates of rates from clinical events which, in the opinion of the EAC, were not well supported by the evidence identified from the clinical literature. Secondly, capital costs and maintenance costs of the Spectra Optia device were not included in the base case results. Thirdly, using 12 subgroups required the company to make assumptions on how the modalities would perform without clinical evidence at that level of granularity. The EAC considered the sensitivity analyses performed by the company were of limited value, because they did not challenge the underlying assumptions of the model or address its limitations.

In the opinion of the EAC, the cost saving potential of the Spectra Optia system, compared with manual exchange, had not been demonstrated with confidence by the company's model. However, the EAC considered that the Spectra Optia system had the following economic benefits which, taken as whole, may be resource saving for the NHS:

- Reduced intervals between procedures. This was included in the model based on good evidence from clinical studies.
- Reduced procedural times leading to reduced use of staff resources. This was included in the model based on good evidence from clinical studies.
- Reduced rates of complications, stroke, and iron overload. This was included in the model, but whilst was not evidenced by clinical studies, was considered plausible by clinical experts.
- Reduced variability in clinical practice, helping to standardize the treatment of patients with SCD on a local and national level (not included in model).
- Improved safety and auditing of exchange procedures (not included in model).
- In some patients, use of depletion-exchange to optimize the treatment with the possibility of reduced RBC consumption (compared with standard exchange, included in model as sensitivity analysis).
- Increased return on capital investment by using also the device in other indications such as plasma exchange apheresis and stem cell harvesting (not included in model).

External Assessment Centre commentary on the robustness of evidence submitted by the company

The comparative clinical studies reported were generally retrospective and did not adequately control for potential confounding and bias. The single-armed studies reported only absolute rather than comparative data. The *de novo* economic model relied on data from these studies or from additional studies whose identification had not been described and which had not been critically appraised. Clinical experts provided anecdotal evidence to support Spectra Optia based on their experience.

Summary of any additional work carried out by the External Assessment Centre

The EAC undertook additional economic analysis using the company's model but adding the costs of the technology, as well as including revised figures for key resource use (primarily chelation costs). The analysis suggested that, compared with manual RBCx, the Spectra Optia system was likely to be cost saving in patients with no or mild iron overload, but cost incurring in patients with moderate or severe iron overload. This analysis was subject to the same uncertainties as the company's model.

The EAC corresponded with the NHS Blood and Transplant Therapeutic Apheresis Services (TAS) regarding the potential for alternative provision of the Spectra Optia. Using this service a red cell exchange undertaken in one of five TAS Units is [redacted], with additional charges applying for out of hours or extra-departmental activity.

Regarding the estimated size of patient population that could benefit from Spectra Optia; the EAC reviewed data in the National Haemoglobinopathy Registry (NHR), and personal communications of confidential business cases and concludes that the upper limit of unmet need for automated RBCx is 5 to 10% of all patients with SCD. In addition, geographical inequalities of access mean that SCD patients are being referred from the Scottish borders, the South West of England and North Wales for transfusion therapy in London.

EAC conclusion

There is a lack of prospective, controlled trials to demonstrate the clinical superiority of the Spectra Optia system to manual RBCx in clinical outcomes. However, a lack of evidence is not the same as evidence of no effect, and the EAC considers there are sufficient grounds, provided by clinical experts experienced in the use of the system, to believe that the Spectra Optia provides important additional benefits over manual RBCx. One of these

benefits is the ability of the system to provide improved standardised care at a local and national level. Alternative methods of delivery, such as through TAS, could improve patient access to effective RBCx and reduce geographical inequalities.

Abbreviations

AIM	Automated interface management system
BCSH	British Committee for Standards in Haematology
CI	Confidence interval
EAC	External assessment centre
HbS%	Percentage of patient's total haemoglobin that is sickled
IHD	Isovolaemic haemodilution
MRI	Magnetic Resonance Imaging
NHR	National Haemoglobinopathy Registry
NUTH	Newcastle upon Tyne Hospitals NHS Foundation Trust
RBC	Red blood cells
RBCx	Red blood cell exchange transfusion
SCA	Sickle cell anaemia
SCD	Sickle cell disease
SCS	Sickle Cell Society
TUT	Top up (simple) transfusion
WHO	World Health Organisation

2. Background

2.1 Overview and critique of company's description of clinical context

2.1.1 Critique of company's description of the background condition

The EAC considered that the background to the condition supplied by the company (company submission, Section 3.1) was an accurate and concise description of the pathophysiology of sickle cell disease (SCD). The EAC has cross-referenced the information for factual accuracy and has not detected any specific issues. However, the EAC would draw attention to the final subsection, where the evidence base for simple 'top up' transfusion and the relative benefits of exchange and top up transfusions are discussed. Whilst the EAC does not disagree with this content, the EAC would question its relevance to the scope of the decision problem. This issue is discussed in Section 2.3.4.

2.1.2 Overview of relevant clinical guidelines

The company discussed the relevant clinical guidelines for the management of SCD in children in Section 3.2. The EAC has confirmed the contents of this section were accurate, but identified an additional guideline that was of potential relevance to the decision problem. This was the guideline "Management of Sickle Cell Disease in Pregnancy" by the Royal College of Obstetricians and Gynaecologists (green top guideline) [24]. The main relevant recommendations of this guideline were:

- Routine prophylactic transfusion is not recommended during pregnancy for women with SCD.

- If acute exchange transfusion is required for the treatment of a sickle complication, it may be appropriate to continue the transfusion regimen for the remainder of the pregnancy.

The clinical guideline (CG143) by the National Institute for Heath and Care Excellence (NICE) "Sickle cell acute painful episode: management of an acute painful sickle cell episode in hospital" [14], cited by the company, did not refer to the use of automated or manual RBCx and was therefore not relevant to the decision problem, as the company has recognised.

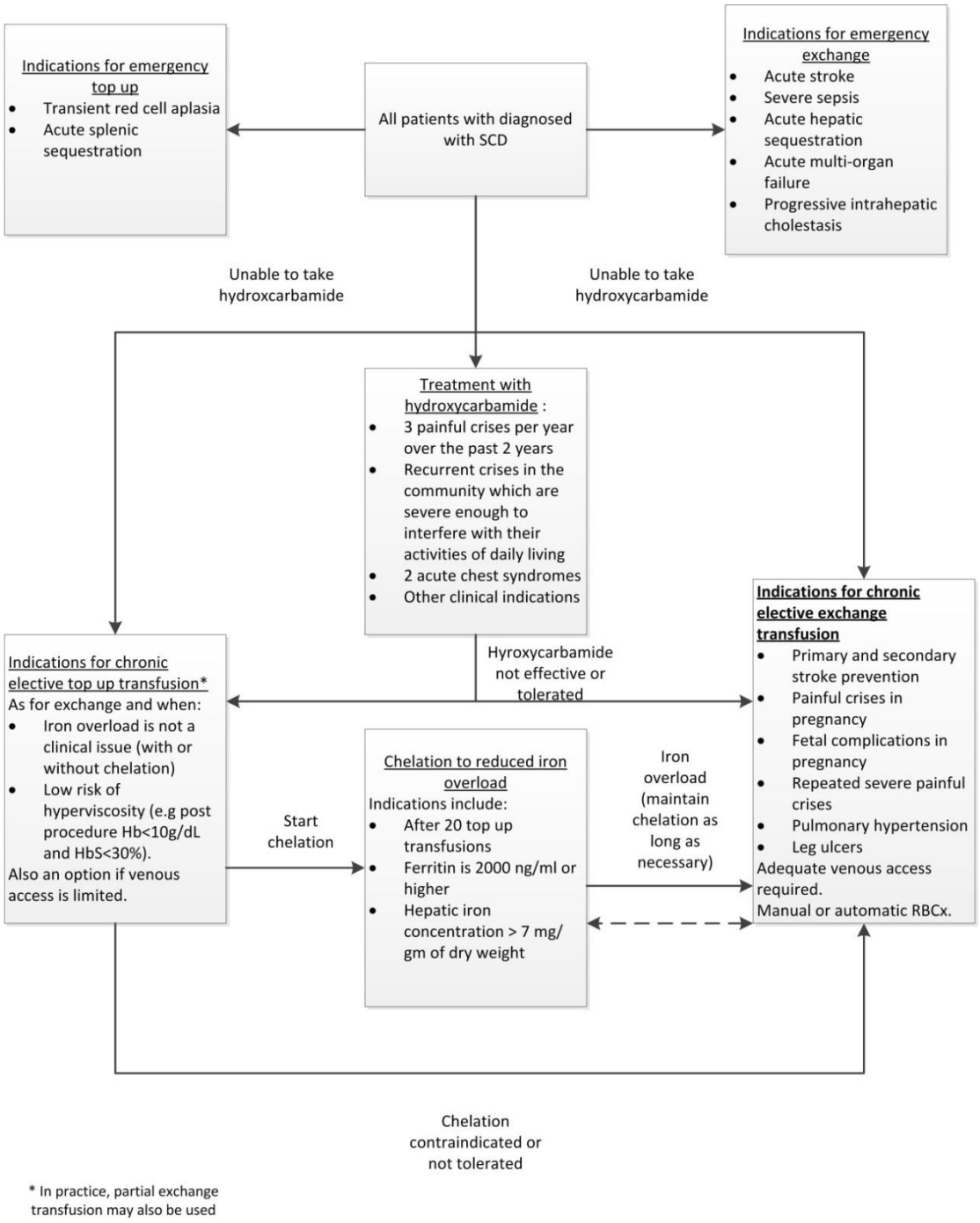
2.1.3 EAC's interpretation of clinical care pathway

The EAC considered that the company's interpretation of the clinical care pathway, described in Section 3.3 of the submission, was an accurate description of current care pathways within the NHS of England and Wales.

The EAC has summarised the patient pathway for people with SCD in Figure 2.1. This has been created using information from national clinical guidelines [25, 26] and feedback from clinical experts (see EAC Correspondence Log). In summary, emergency treatment with top up or exchange transfusion may be used as a one-off or occasionally in patients with SCD for the indications listed. If SCD becomes more chronically symptomatic, then treatment with hydroxycarbamide (hydroxyurea) is an option. However, approximately 25% of patients are unable to take hydroxycarbamide (because of contraindications or because they cannot tolerate it) or remain refractory to treatment. Additionally pregnant or breastfeeding women, or people of both sexes planning to conceive, should not take hydroxycarbamide. For these patients, elective transfusions are an option [25, 26].

The initial choice of transfusion therapy depends on a range of factors dependent on clinical status and, in practice, local facilities. In general, top up transfusions are suitable if the main purpose of treatment is to manage anaemia, and 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 require chelation therapy at some stage (typically after around 20 transfusions). The alternative is red blood cell exchange (RBCx) transfusion which is considered to be 'iron neutral' because packed RBC are used to replace the patient's blood in an isovolaemic manner. This can be done using manual or automated techniques, of which the Spectra Optia system belongs to the latter. It is the differences in these methods (in bold font in Figure 2.1) which is the focus of the scope.

Figure 2.1. *Schematic flow chart illustrating patient pathways for people with SCD*.



2.1.4 Issues relating to current practice

In section 3.4 of their submission, the company correctly identified that "Local practice is likely to vary significantly with regard to availability, infrastructure and organisation". In the following sentence, the company stated that "Publically available NHS procedures for manual exchange appear to be very consistent". This statement is unreferenced and it is not clear what it means, considering there appears to be widespread variation in how manual RBCx is performed (see summary of EAC Clinical Expert feedback in Table 3.9 and full transcripts in the EAC Correspondence Log).

2.1.5 Potential changes to pathway introduced by Spectra Optia

The EAC has agreed with the company's interpretation on potential changes to the patient pathway, which would be potentially minimal as the Spectra Optia system would be a direct replacement for manual RBCx (see Figure 2.1). However, the Spectra Optia is a multifunctional system that has applications for bone marrow processing, mononuclear and granulocyte collection, and therapeutic plasma exchange. Although these indications are out of scope, it is possible that these would open up the possibility for use of the system in a setting other than specialist secondary or tertiary care, such as the NHS Blood and Transplant Therapeutic Apheresis Services (TAS) units [27]. This might allow for the localised treatment of people with severe SCD in regional centres, thus preventing the need for travelling long distances. This possibility is discussed in Section 4.5.3.

2.2 Overview of company's description of ongoing studies

In Section 5.1 of their submission, the company reported they had searched clinicaltrials.gov and ICTRP (International Clinical Trials Registry Platform of the World Health Organization) and identified no relevant ongoing studies of the Spectra Optia system for the treatment of SCD.

The EAC has independently repeated these searches and can confirm no relevant trials were identified. During correspondence with the clinical experts, the EAC discovered that, in their opinion, future prospective, comparative studies were unlikely because of a lack of clinical equipoise (see Section 6).

2.3 Critique of company's definition of the decision problem

2.3.1 Population

The population specified in the scope was "Sickle cell disease patients requiring a medium or long-term *exchange transfusion regime*" [1] (EAC's emphasis). However, this had been altered in the company's statement of the

decision problem (Table A1) to state “Sickle cell disease patients requiring a medium or long-term *transfusion regime*”.

This alteration in wording, where the word ‘exchange’ has been omitted, is important because it enables patients requiring top up transfusions to be included within the definition of population in the scope. However, the original scope clearly and specifically describes patients requiring exchange transfusion as the population of interest.

The other aspect of the population scope is the timeframe over which exchange transfusions are performed. The EAC has clarified that “medium or long-term” refers to repeated elective treatment for SCD, meaning that patients who have received transfusions for one-off emergencies or single elective procedures (for instance, before surgery) are out of scope. Patients receiving one-off treatments are listed as an exclusion criterion by the company (company submission, Table B1). However, a small number of the included studies included a mix of chronic elective and emergency patients, and in most cases, it was not possible to disaggregate these data. As the company did not always exclude these mixed studies (and the EAC agrees this would lead to a smaller evidence base), these studies have been included in this report. The EAC has highlighted which studies are affected in Section 3.5, but it is not possible to predict how the inclusion of out of scope patients might impact on results.

2.3.2 Intervention

The company provided the EAC with a current EC certificate from BSI (British Standards Institution), a UK Notified Body, dated 28 January 2015, with expiry date 28 July 2018. This shows the manufacturer’s quality assurance system meets the requirements of the Medical Devices Directive (MDD) 93/42/EEC in respect of the design, development and manufacture of automated blood cell separators and their related components. The company also provided the manufacturer’s EC Declaration of conformity, dated 28 May 2014, showing MDD classifications for the Spectra Optia apheresis system (class IIb) and all disposable components (either class I, class IIa or class IIb).

The intervention stated in the scope is simply “Spectra Optia Apheresis System” [1] which was correctly identified by the company. When combined with the population specified in the scope it is clear the intervention is indicated for patients with SCD in whom chronic RBCx exchange is of potential benefit.

In company submission Table A1 (statement of the decision problem), the company included the Cobe Spectra device as an intervention. The Cobe Spectra system was the predecessor to the Spectra Optia system, and its

inclusion in the submission was intended to increase the evidence base with which to assess the Spectra Optia system. In company submission section 2.1 and Table A2, the company has provided information about the two systems and states that they are “essentially equivalent devices”. In addition, the company briefly discusses three comparative studies that compared the Spectra Optia and Cobe Spectra systems. These were the studies of Perseghin *et al.* (2015) [28, 29], Poullin *et al.* [30], and Turham *et al.* [31]. The company claimed that the results from these studies supported the equivalence of the device and therefore that the Cobe Spectra system should be “included as evidence to support the claims made for the Spectra Optia system”.

The EAC has considered the equivalence of the Cobe Spectra and Spectra Optia systems and agrees that, for most cases, the systems should be considered as equivalent (technical comparison is given in Appendix A). This is because:

- It is clear that the Spectra Optia system has been substantially improved over the Cobe Spectra system; however, these improvements are largely incremental in nature rather than representing a more fundamental change in the technology.

- The EAC has spoken to representatives of the manufacturer of the systems and they have confirmed that the systems are functionally equivalent in terms of efficacy (see EAC Correspondence Log). The Spectra Optia system has additional functionality that potentially improves safety, operator performance, patient experience, and has implications for resource use, but these should not negatively impact on the system’s efficacy compared with the Cobe Spectra system.

- An important technical difference between the systems is the difference in extracorporeal blood volume (185 ml for the Spectra Optia compared with 285 ml for the Cobe Spectra). The EAC has been reassured by the manufacturer this will not lead to a significant performance issues, and in fact would be advantageous for use in children (reducing the need for ‘custom primes’ whereby there is a need to infuse blood into the patient before exchange can begin).This would represent a benefit of the Spectra Optia system.

- Subsequent to the manufacturer teleconference, one clinical expert advised the EAC that the lower extracorporeal volume of Spectra Optia could mean fewer adverse events such as hypotension or fainting (being less of a stress on the cardiovascular system). However, clinicians might give some saline before an exchange transfusion

anyway to reduce these risks. In addition, a lower extracorporeal volume can mean that smaller patients (e.g. younger children) can be offered automated exchange transfusion (see EAC Correspondence Log).This clinical expert feedback therefore supports the company's above claimed benefit that fewer procedures might require the blood prime, since the extracorporeal volume of the Optia is lower than that of the predecessor Cobe Spectra system.

- The EAC does not consider the evidence from the three submitted studies constitutes good evidence of equivalence between the systems. This is largely due to the poor quality of the studies which makes interpretation problematic (see Section 3.5.7).

Another important difference between the systems is that Spectra Optia system has an additional dedicated procedure: that of depletion-exchange. In this procedure, suitable only for use in patients with an adequate haematocrit, an initial volume of red blood cells (RBC) is removed and replaced with a fluid replacement (typically 0.9% sodium chloride solution) before exchange proceeds as usual [26]. This has the effect of reducing the burden of sickled cells and percentage of the patient's total haemoglobin that is sickled (HbS%) before exchange is performed, and potentially reducing the amount of replacement packed RBC required (and thus possibly reducing the potential for alloimmunisation).

Whilst depletion exchange was not explicitly listed as an intervention in the scope, several studies have been included in which this procedure was used as the intervention. The EAC considers that this is appropriate given that exchange/depletion represents an intrinsic element of the Spectra Optia system and might provide additional benefits in some patients with SCD. Additionally, manual RBCx also sometimes involves a depletion stage (see below).

2.3.3 Comparator(s)

The comparator specified in the scope was "Manual red blood cell exchange". The process of manual RBCx can be variable and differs between centres and physicians, and is often tailored to the patient's individual requirements (see EAC Correspondence Log). A published example of a manual exchange involves withdrawing and discarding 500 ml of blood from the patient, and replacing this with 500 ml saline. Then a further 500 ml of blood is withdrawn and discarded and replaced with 2 units of packed RBC [32]. This process can be repeated until the target HbS% is reached. This process is directly comparable to automated RBCx or the depletion-exchange mode of the Spectra Optia.

However, Table A1 of the company submission, indicated that a variation from the scope for the comparator should be included, that of “Simple or ‘top up’ transfusion”. The company has justified this inclusion using the following rationale (as paraphrased by the EAC):

- The “vast majority” of transfusions for SCD are simple top up transfusions. In the submission, this was incorrectly referenced to a review by Smith-Whitley *et al*. (2012) [33], when in fact this exact wording can be attributed to the review by Swerdlow (2006) [32]. As this was an American review it is not clear how relevant this is to UK practice.

- Exchange transfusions have significant advantages over simple top up transfusions, particularly in reducing the risk of iron overload and vaso-occlusive events.

- If patients were switched to RBCx earlier in the disease process then the risks of iron overloading and the requirement for chelation therapy could be substantially reduced (this is unreferenced).

- There is supportive evidence that automated RBCx is superior to both manual RBCx (this is discussed at length later in the document) and top up transfusions.

- Top up transfusions reflect “current practice in the UK” and therefore the scope should be amended to reflect this (this is unreferenced).

The EAC considers there are two issues to consider with the company’s rationale. The first concerns the comparative efficacy of RBCx and top up transfusions, and the second concerns what is used in standard practice in the UK.

For the first point, the EAC recognises the advantages of RBCx (manual or automated) over top up transfusions. The treatment of SCD has two main targets, which are to treat anaemia and increase oxygen carrying capacity of the blood, and to reduce the incidence of vaso-occlusive events and associated complications (such as stroke, painful crises, and acute chest syndrome). Top up transfusions will treat the former, but will have less benefit for the latter. This is not a matter of dispute and is reflected by national guidelines such as those by the Sickle Cell Society [26] and the British Committee for Standards in Haematology (BCSH) [25]. However, this should be considered in the following context:

- Top up transfusions and RBCx are not mechanistically equivalent procedures. During top up transfusions, donor RBC units are simply

added to the the patient which has the effect of diluting the proportion of sickled cells and HbS. In comparison, RBCx using any method removes blood (including sickled cells) and replaces it with donor RBC units. Therfore the effect size for clinical outcomes, for instance in achieving HbS targets or avoiding iron overload, are expected to be different. In this context, inclusion of top up transfusions as a comparator is not a valid clinical comparison.

- Top up transfusions and RBCx have subtly different indications and relative contraindications. In general, top up transfusions are preferred when haemoglobin levels are low, to treat anaemia. In contrast, RBCx is preferred in most other clinical indications for the elective treatment of SCD. Guidelines from the Sickle Cell Society state “The risk of hyperviscosity is an important consideration in deciding the optimal transfusion regime [top up transfusion or RBCx]” [26]. This guideline recommends top up transfusions should be avoided if it would result in a post-transfusion haemoglobin level of 10 to 11 g/dL, particularly if the proportion of HbS is 30% or more. The British Committee for Standards in Haematology (BCSH) state red cell apheresis is “a better option where transfusional iron overload from simple (top up) transfusions could be expected to be a problem” [25].

- Lower HbS targets (for example HbS of 30%) are generally more difficult to achieve when top up transfusions are used compared with full RBCx (see EAC Correspondence Log).

- The company suggested that patients might have better outcomes if they were specifically switched to automated RBCx earlier in their disease process. However, this statement was not referenced and is not described elsewhere in the scope or in the clinical section of the submission, and is therefore not substantiated.

For the second point, above, the EAC is aware of the possibility that there is limited access to RCBX within the NHS and treatment of SCD may be suboptimal in some areas. However, this is not an argument for the adoption of the Spectra Optia system *per se*, as manual RBCx could also be implemented. Therefore a comparison of the Spectra Optia system and manual RCBX is still required.

In summary, the EAC considers that simple or top up transfusions should remain out of scope because they are not equivalent to the intervention and under current guidelines they have subtly different clinical indications. The company’s argument that in many instances automated RCBX is superior to top up transfusions is not a valid argument to change the scope, and instead a comparison with manual

RCBX is required. Therefore, studies which have compared the Spectra Optia system with simple or top up transfusions were disregarded by the EAC with respect to the main decision problem (although they may provide supplementary information).2.3.4. Outcomes

In the scope, ten primary outcomes and five secondary outcomes were listed. These outcomes are a mixture of physiological or pathological measurements (in some cases could be regarded as surrogate outcomes), clinical outcomes, and outcomes associated with resource use and patient experience.

The primary outcomes were: Percentage of total haemoglobin that is sickled (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; and Frequency of top-up transfusion required to treat sickle cell complications. The company identified published evidence on most of these with the exception of the clinical outcomes, staff time and staff group/grade, and quality of life.

The secondary outcomes were: Ease of venous access, bruising and haematoma; Device-related adverse events; Hospital admissions; Donor blood usage; BMI and growth in children. The company identified published evidence on all of these with the exception of BMI and growth in children.

The company also requested that an additional outcome should be reported where available, that of alloimmunisation rates and donor [blood] exposure. The reason stated for this was that alloimmunisation is a known adverse effect of transfusion therapies and that the risk increases with increased exposure to donor blood. The EAC accepts that the addition of alloimmunisation to the scope as a safety outcome is reasonable.

2.3.5 Cost analysis

In the scope, the cost comparator is defined as “Manual red blood cell exchange” only [1]. However, the *de novo* model reported in the economic submission included top up transfusions as an arm. This, and issues concerning the time horizon, payer perspective, and discounting are discussed in Section 4.

2.3.6 Subgroups

Six subgroups were included in the scope. These were: Children and adults at high risk of stroke; Pregnant or breastfeeding women; Patients with iron

overload; Patients with acute chest syndrome; Patients with multi-organ failure; and Children.

The company identified relevant patient subgroups in their description of studies (for instance company submission Table 3 and Tables of studies B6a to B6ad) but otherwise did not treat the subgroups individually. Data on some of the subgroups was limited (for example one study on pregnancy) or absent (for example patients with acute chest syndrome or multi-organ failure). There was also some ambiguity on the definition of subgroups (for instance, what is the defined age of a child?), and in some instance the studies reported on mixed populations of subgroups which were not possible to disaggregate. These issues are discussed further in Section 3.6.5.

2.3.7 Special considerations, including issues related to equality

In the scope, three groups with protected characteristics (Equality Act, 2010) were identified. These were:

- People with disabilities (inability to carry out normal day-to-day activities) because of SCD.
- Some religious groups (principally Jehovah's Witnesses, who are opposed to blood transfusion).
- People of black African or Caribbean descent (who have the highest prevalence of SCD).

In addition, the company highlighted pregnant women are also at risk of additional complications of SCD (pregnancy and maternity is a protected characteristic under the Equality act 2010).

The scope and company submission also highlighted another area of potential inequality, which is an inequity of access to the highest standards of care due to regional variation in the provision of treatment. Although this is likely to be driven by the underlying prevalence of the disease, with highest rates in London [34], patients living far from treating hospitals (London, Manchester, and Birmingham [paediatrics]) may receive suboptimal treatment or face significant transport issues. Should the Spectra Optia system be adopted, issues of regional inequality should be considered (see Section 5).

3 Clinical evidence

3.1 Critique of the company's search strategy

The PRESS (Peer Review of Electronic Search Strategies) Checklist was used to inform the critique of the company's search strategy [35]. The PRESS checklist is an evidence-based tool to critically appraise literature search strategies. The PRESS project was funded by the Canadian Agency for Drugs and Technologies in Health (CADTH) and this approach to peer reviewing search strategies is supported by the Cochrane Collaboration's Information Retrieval Methods Group [36].

For the purpose of this critique, it was assumed that the company intended to identify studies on Spectra Optia, Cobe Spectra or manual exchange transfusion, although the submission was not clear on this issue.

The company conducted two separate bibliographic database searches. The company found this initial set of searches to be too restrictive, with relevant studies being excluded. In the light of the missed relevant studies, the initial strategy was revised, and a second set of searches were conducted.

The information resources searched were appropriate for a search for published clinical evidence. They included the resources indicated as a minimum requirement on the NICE Company's submission template: MEDLINE, MEDLINE In-Process, Embase, and Cochrane Library. In addition, for the initial searches, the company searched Scopus, Pubmed, Econlit, and Web of Science (Science Citation Index Expanded / Conference Proceedings Citation Index- Science). The manufacturer (Terumo) provided the company with a database of complaint information. For the second set of searches Scopus, Science Citation Index Expanded and Conference Proceedings Citation Index-Science were not searched due to time constraints. This meant that there was inconsistency between the 2 sets of searches, and that the selection of resources for the second set of searches was more limited than the first. This impacted on the robustness of the second set of searches.

The MTEP Methods guide indicates that search sources will include registers or databases of ongoing clinical trials. No reference is made to a search of trial registers in either the section on Identification of Studies (submission, section 7.1) or the search Appendices (submission, sections 10.1 and 10.2). Elsewhere in the submission, the company states that "there are no ongoing studies…listed on trials websites (clinicaltrials.gov or ICTRP)" (submission, section 5); this does seem to indicate that some sort of search had been carried out, but no further details were given. It was therefore not possible to assess the appropriateness of any trial register searches for ongoing or unpublished studies.

The company searched database resources which index some conference proceedings, for example Embase and Conference Proceedings Citation Index-Science. The submission also refers to a hand-search of conference proceedings (submission, section 7.1) but full details and reproducible search methods were not included. Subsequent communication with the company confirmed that additional hand-searches had been carried out for specific conference proceedings. The search methods for these were focussed (consisting of a search on the term 'exchange' across the proceedings document, with no additional variant terms searched on), but the number of individual proceedings searched was relatively high. Conference proceedings were searched if they included a relevant study which had been identified by the database searches. Although this resulted in the relatively high number of proceedings which were searched, it also meant that there were gaps in the conference coverage (for example, the company searched abstracts from the British Society for Haematology annual meeting for the years 2012, 2014 and 2015, but not for 2013).

A description of the searches for published studies was given in the submission, section 7.1.1. In the submission section where the company is asked to describe the strategies used to retrieve relevant clinical data from unpublished sources (section 7.1.2), no description was given. The company states that "No unpublished data is reported. None was identified by the manufacturer", but the strategies used are not described. Details of search strategies for published clinical evidence were provided in the submission, Appendix, section 10.1. No separate searches were carried out to identify adverse events. This was appropriate as the searches for clinical evidence were not limited by study design or outcome and would therefore have identified studies which reported on adverse events.

The MTEP Company's submission template indicates that search methods for both published and unpublished evidence should be transparent and sufficient detail should be provided to enable the methods to be reproduced. The main bibliographic database searches fulfil this requirement. There was some lack of detail and clarity in the reporting (for example, the interface was not provided for the Econlit search, and the details for the Cochrane Library search did not make explicit which constituent databases were searched – submission, section 10.1) but the bibliographic database strategies were provided in full, enabling reproduction.

The submission referred to or indicated other search activities where methods were not transparent and reproducible. These include the conference hand-searches referred to in the submission section 7.1.1, the trial register searches implied by the statement in the submission section 5.1 ("There are no ongoing studies known to the manufacturer or listed on trials websites

(clinicaltrials.gov or ICTRP)"), the Google searches which were referred to as a source of studies in the submission section 7.2.2, and the search of MHRA which was referred to in the submission section 7.7.3. The reporting of methods in the submission would have been enhanced by inclusion of explicit, reproducible methods for all search sources. For the searches where full details were not provided in the submission, it was not possible to assess the quality of, or reproduce, the company searches.

The search strategies were structured into concepts, reflecting the population and interventions of interest. The construction of strategies meant that at times it was not clear what the searcher was aiming to do (for example the second Ovid MEDLINE strategy, submission, section 10.1.4). There was also some redundancy in the inclusion of terms (for example, the same terms occurring in 2 sets of terms which are being combined as AND), which added to an overall lack of clarity.

No errors were identified in the use of Boolean. Where database functionality allowed, the strategies were mostly constructed using explicitly specified subject headings and free-text searches. Proximity operators were used correctly, although they seemed narrow. Given the low numbers of records retrieved for screening, the sensitivity of the search could potentially have been enhanced by broadening the proximity operators.

The strategies included key subject headings for the population and interventions of interest. The sensitivity of the search would have been enhanced by including a broader range of subject headings. For the population terms for example, subject headings available in MEDLINE and Embase for forms of sickle cell disease (such as Hemoglobin SC Disease/ in MEDLINE) could have been included. Similarly, the intervention terms could have included additional potentially useful subject headings (such as Exchange Transfusion, Whole Blood/ in MEDLINE).

The strategies included key free text terms for the population and interventions of interest. However, the sensitivity of the search could have been enhanced by including a wider range of free-text terms to capture potentially relevant variant descriptions of the concepts of interest, and by using a less restrictive approach to combining terms. For the population for example, the strategies could have included free text terms for different forms of sickle cell disease (such as Hemoglobin SS, Hemoglobin SC, Hemoglobin Sβ0 thalassemia, Hemoglobin Sβ+ thalassemia, Hemoglobin SD, Hemoglobin SE). For the intervention concept, the way the strategy combined terms seemed highly restricted. As an example, although the MEDLINE and Embase strategies contain various permutations of potentially relevant intervention terms, the way the terms are combined means that phrases such

as ‘automated exchange transfusion/s’ or ‘manual exchange transfusion/s’ are not covered by the search terms. Phrases such as these would seem to be potentially highly relevant to the interventions of interest; by taking such a focused approach there was an increased risk of missing relevant studies. The MTEP Methods Guide indicates that the purpose of the identification of studies is to ensure a comprehensive evidence base is available to the Committee. In this context, the robustness of methodology would have been enhanced by taking a more sensitive approach to search design; as the number of records retrieved for screening was relatively low there would seem to have been scope for this.

No spelling errors were identified. The use of truncation was mainly appropriate, though the strategies would have been enhanced by additional use in some instances (e.g. truncation of the device name to retrieve potential variants such as ‘devicenameTM’ and truncation of the term ‘exchange transfusion’ in the Cochrane Library, Econlit and Web of Science searches in order to include the plural ‘exchange transfusions’).

The choice of search field was mainly appropriate. The sensitivity of Ovid MEDLINE searches could have been potentially enhanced by including searches across the keyword heading word field; similarly the Embase searches could have included searches across additional fields, for example the keyword field and the device name field. The choice of search field for the Cochrane searches seemed inappropriate for some of the constituent databases. One single search was carried out across the Cochrane Library for all databases and searches were limited to the title / abstract / keyword fields. This latter limit is not appropriate for a search of the DARE, HTA and NHS EED databases, as (despite what the field limitation suggests) it does not include a search across abstracts in these resources; in effect for these three databases the strategy searched in the title and keyword fields only.

Line numbers appear to have been combined correctly. However due to a lack of clarity in the strategy structure it was not always possible to be certain of the searcher’s intentions (for example the second Ovid MEDLINE strategy, submission, section 10.1.4.).

There were some differences in strategy adaptations between search sources for which the rationale was not clear. For example, the MEDLINE strategy for the second set of searches differed in key ways from the equivalent Embase search (resulting in a more restricted search), and the second EconLit search did not include the term ‘apheresis’ whilst other strategies did.

Searches were not restricted by date or language (though the submission selection criteria restricted to English language studies and studies published

since 1993). This was appropriate as the language and date selection criteria could be applied at screening stage. No study design filter was used; this was appropriate for a review where the selection criteria were not restricted by study design. Search dates were explicitly reported: the initial literature search was conducted on 03 June 2015; the second, extended literature search was conducted on 09 and 10 June 2015. The currency of the searches at the time of submission was therefore very good.

The EAC reproduced the company bibliographic database searches, using the details as reported in the submission, section 10.1.4. Searches were not carried out for the company search activities where insufficient information was provided to enable replication. As far as possible, the bibliographic database searches were replicated exactly as reported. Where the EAC had to use an alternative interface due to access differences (for example, when searching Econlit) the company strategy was translated as closely as possible. The strategies used by the EAC when re-running the company's search and the volume of results identified are reported in full in Appendix B Some minor assumptions were made where the reported methods lacked clarity; these are made explicit in the Appendix. The EAC obtained a slightly different yield on repeating the company's search strategy to that indicated by the PRISMA diagrams in the submission. However, the submission did not include result numbers for several of the strategies, so it was not possible to check if the PRISMA was an accurate reflection of retrieved record numbers, or to identify the reason for the difference.

3.1.1 EAC's additional searches

Searches were conducted by the EAC in order to retrieve any studies that might have been missed by the company search strategies.

A strategy was developed for MEDLINE (Ovid interface) to identify evidence on the effectiveness of Spectra Optia, Cobe Spectra, or manual red blood cell exchange transfusion in sickle cell disease patients.. The strategy was devised using a combination of subject indexing terms and free text search terms in the title, abstract and keyword heading word fields. The search terms were identified through assessment of the company strategy, discussion between the research team, scanning background literature, browsing database thesauri and use of the PubMed PubReminer tool (http://hgserver2.amc.nl/cgi-bin/miner/miner2.cgi). The final strategy for Ovid MEDLINE is shown in Figure 3.1.

Figure 3.1. *EAC search strategy for Ovid MEDLINE and MEDLINE In-Process.*

1 anemia, sickle cell/ (17359)

2 sickle cell$1.ti,ab,kf. (19260)
3 (SCA or SCD).ti,ab,kf. (11679)
4 (h?emoglobin S or h?emoglobin SS or SS disease$1).ti,ab,kf. (1774)
5 (HBS or HB-S or HBSS or HB-SS).ti,ab,kf. (10918)
6 Hemoglobin, Sickle/ (2754)
7 (h?emoglobin adj3 thalass?emia).ti,ab,kf. (768)
8 (sickle adj3 (an?emia$ or h?emoglobin)).ti,ab,kf. (8190)
9 Hemoglobin SC Disease/ (572)
10 (h?emoglobin SC or SC disease$1).ti,ab,kf. (397)
11 (HBSC or HB-SC).ti,ab,kf. (654)
12 (h?emoglobin SD or SD disease$1).ti,ab,kf. (153)
13 (HBSD or HB-SD).ti,ab,kf. (29)
14 sickling.ti,ab,kf. (1287)
15 (drepanocyt$ or microdrepanocyt$).ti,ab,kf. (363)
16 meniscocyt$.ti,ab,kf. (3)
17 or/1-16 (41804)
18 Exchange Transfusion, Whole Blood/ (4140)
19 Erythrocyte Transfusion/ (6760)
20 blood component removal/ (3834)
21 ((red blood cell or red blood cells or red cell or red cells) adj3 exchang$).ti,ab,kf. (472)
22 ((RBC or RBCs or RC or RCs) adj3 exchang$).ti,ab,kf. (96)
23 ((erythrocyte$ or normocyte$) adj3 exchang$).ti,ab,kf. (476)
24 (RBCx or RBCE or RCX or RCE).ti,ab,kf. (408)
25 (ARCET or RCET).ti,ab,kf. (10)
26 erythroexchange$1.ti,ab,kf. (6)
27 erythrocytapheresis.ti,ab,kf. (150)
28 (exchang$ adj3 (transfusion$1 or blood)).ti,ab,kf. (5925)
29 (EBT or EBTs).ti,ab,kf. (770)
30 ((chronic or exsanguinatio$ or substitution or total or replacement) adj transfusion$1).ti,ab,kf. (533)
31 cytapheresis/ (302)
32 (apheresis or cytapheresis or cytopheresis or pheresis).ti,ab,kf. (5795)
33 ((automat$ or auto) adj3 exchang$).ti,ab,kf. (266)
34 (blood cell$1 adj3 (separator$1 or separation or separating)).ti,ab,kf. (545)
35 (optia$ or cobe$ or terumo$ or caridian$ or gambro$).ti,ab,kf. (1603)
36 ((spectra or spectrar or spectratm or spectrartm) and (exchang$ or transfusion$1)).ti,ab,kf. (5663)
37 (manual$ adj3 exchang$).ti,ab,kf. (64)
38 or/18-37 (31395)
39 17 and 38 (975)
40 exp animals/ not humans/ (4063890)
41 (news or comment or editorial).pt. (1050549)
42 39 not (40 or 41) (935)
43 limit 42 to (english language and yr="1993 -Current") (640)

44 remove duplicates from 43 (622)	
Key to Ovid symbols and commands	
$	Unlimited right-hand truncation symbol
$N	Limited right-hand truncation - restricts the number of characters following the word to N
?	Wildcard symbol
ti,ab,kf.	Searches are restricted to the Title, Abstract, Keyword Heading Word fields
adjN	Retrieves records that contain terms (in any order) within a specified number (N) of words of each other
/	Searches are restricted to the Subject Heading field
exp	The subject heading is exploded
pt.	Search is restricted to the publication type field
or/1-3	Combines sets 1 to 3 using OR

The search was comprised of two concepts:

1) Sickle Cell Disease. Search lines 1 – 17.

2) Exchange transfusion. Search lines 18 – 38.

The concepts were combined as follows: Sickle Cell Disease AND Exchange transfusion.

Reflecting the submission selection criteria (submission, Table B1), non-English language publications and studies published before 1993 were excluded from the search results. The strategy also excluded animal studies using a standard algorithm. Publication types which were unlikely to yield study reports were also excluded: news, comments, and editorials. The search was not restricted by study design.

In the context of the limited time available to the EAC, the EAC review team decided that a relatively focused approach should be taken to the searches in order to keep record numbers to a level which was manageable for screening within project resources. The need for search sensitivity was therefore balanced with the need for precision, and this pragmatic context informed the search strategy development. This included the decisions, for example, to not search on non-specific transfusion terms, and to use narrow proximity operators and phrases to focus free-text search lines. The pragmatic decisions taken may have meant some increase in the risk of missed relevant studies; the review team felt however that the sensitivity of the searches (combined with supplementary approaches such as reference checking) remained appropriate to the project context.

The EAC searched all of the resources explicitly reported in the company submission as included for the initial set of searches, apart from Scopus (excluded for pragmatic reasons, and because not included in the company's second set of searches). The EAC also searched additional resources including 2 additional economics resources (HEED and CEA Registry), 3 trial registers, and websites of relevant professional and patient organisations. Records of abstracts presented at annual conferences (past 3 years) were sought for the leading three worldwide conferences where clinical evidence on Spectra Optia may have been presented (as determined in a meeting with NICE and the company). The selection of websites to search was informed by the list of external organisations identified on the NICE final Scope document for the technology.

The MEDLINE strategy was translated appropriately for other search sources. Reflecting the relatively focussed search context referred to above, the review team decided that Emtree subject headings would be searched as major descriptors only. Again, this may have increased the risk of missed relevant studies, but the review team felt it was appropriate to the project context. The PubMed search was restricted to just those records not fully indexed in MEDLINE.

Results of the searches were downloaded in EndNote reference management software and deduplicated using several algorithms. For information resources where interface functionality did not facilitate efficient downloading into EndNote, results were downloaded into Word for assessment.

Strategies (including search dates and interfaces) for all search sources and volume of results returned are included in Appendix C.

3.2 Critique of the company's study selection

The study selection applied by the company (outlined in table B1 of the company submission) was generally consistent with the scope specified by NICE and identified studies according to the relevant population, intervention and outcomes.

The company appropriately identified that chronic programmes of treatment were to be included, whilst treatment for sickle cell crisis emergencies were to be excluded. However, the differing indications for each of these treatment programmes were not specified within the selection criteria. One-off treatments i.e. emergency treatments were correctly identified as out of scope.

The company devised and performed two structured literature searches. They acknowledged that the manufacturer provided a small number of references

which were not identified in the initial literature search. Therefore, a broader second literature search was performed to capture the additional references. These two literature searches were conducted separately and both appropriately followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) methodology to report on the studies identified [37]. The selection of the records was conducted based on title and abstract by two reviewers independently. The company specified that "Due to time constraints and the level of topic-specific understanding required the project lead made a final decision on inclusion of full text papers".

3.3 Included and excluded studies

3.3.1 Company's included and excluded studies

The company stated that of the retrieved records, there were "33 studies in total included in the clinical evidence review, of which 3 contain information solely relating to adverse events". However, there are inconsistencies within the company submission as a total of 34 studies were identified, with 30 'primary study references' in Table B3, and 4 studies relating to adverse events in Table B10a-d. However, it is evident that in 5 cases, 2 separate studies had been combined and tabulated as one 'primary study reference' within Table B3 of the company submission, making 39 unique studies presented in total.. It is not clear, which of the 4 studies relating to adverse events in tables B10a-d was the additional study to the above company statement, nor where it came from.

The EAC replicated the company's search strategy and applied the selection criteria in order to validate the list of relevant studies. The EAC filtered retrieved studies according to the criteria described in Table B1 of the company submission with further clarification of elective and emergency apheresis indications specified by the British Committee for Standards in Haematology (BCSH) [25]. This filtering stage was carried out in duplicate by two researchers. Filtering was performed firstly through reading the study title, and then through reading abstracts where necessary. If the study could not be excluded from examination of the abstract, the full text article was acquired. The EAC's filtering and selection results from the replicated search strategy are illustrated as a PRISMA flowchart in Figure 3.2. From the EAC replicated search strategy, it was apparent that 4 records the company had reported in the company submission had not been identified from the search results [8, 38-40]. The replication of the search strategy required a number of assumptions to be made which also may provide an explanation for the absence of these 4 records. The company highlighted in their PRISMA diagram (Figure 1 of the company submission), that an additional 18 records were found from additional sources (scoping searches, manufacturer). This

may also account for these 4 records. It is also not clear in the clinical submission which studies were identified by the search strategies and which were identified from these additional sources.

Through independent searching and filtering of 405 records, the EAC retrieved 28 studies, 1 of which was presented by the company in table B10d of their submission as a study solely relating to an adverse event (alloimmunisation) [41].

Two studies included in the company submission were solely on manual exchange [22, 42]; and were excluded by the EAC as they did not meet the inclusion criteria of Spectra Optia or Cobe Spectra as the intervention (Table B1 of the company submission). One 'primary study reference' in Table B3 of the company submission (relating to two separate studies) assessed a mixed population including indications for both emergency and elective apheresis procedures [28, 29]. On evaluation of these studies, it was not possible to disaggregate the data for elective procedures only and these studies were therefore excluded by the EAC, as per the selection criteria.[43] Three further studies, presented by the company in tables B10a-c of their submission as studies solely relating to adverse events, did not state the name of the technology used for apheresis and were therefore excluded during the literature sift by the EAC on this basis [44-46]. It has since been confirmed by the company that these studies were conducted using the Cobe Spectra or Spectra Optia systems. A summary of these studies can be found in Table 3.1.

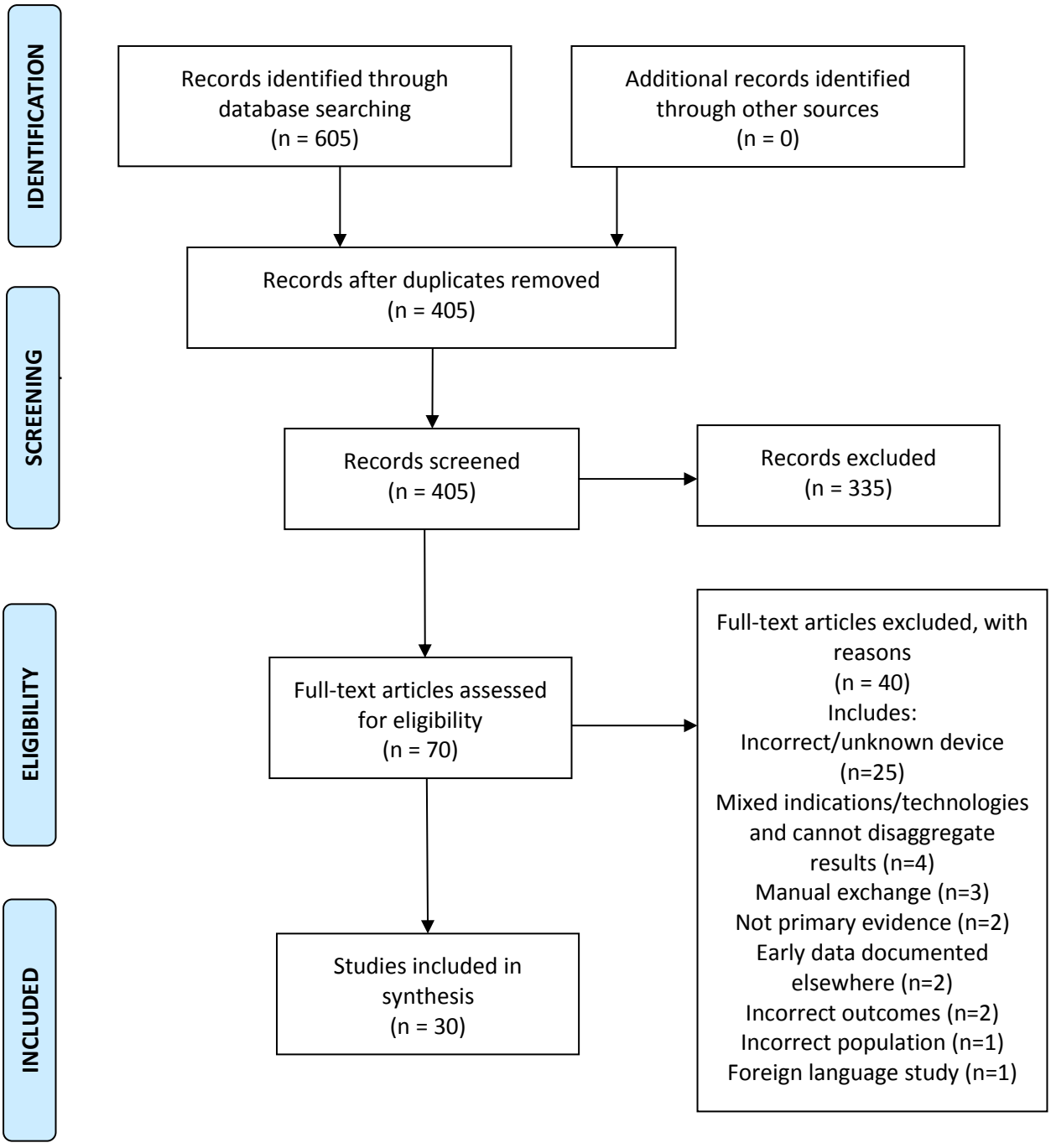
An additional 2 studies were identified from the replicated literature search which were included by the EAC, but excluded by the company. Both of these studies were case series, one of which was a single arm study using Spectra Optia [17], and the other compared the use of Spectra Optia with Cobe Spectra [16]. These studies fulfilled the inclusion criteria and were therefore included by the EAC. As these studies were identified from replicating the company's literature search, it is expected that these studies were found by the company but were considered to be out of scope for the clinical evidence. It is not clear as to why these studies were excluded by the company. These additional 2 studies can also be found in Table 3.1.

Table 3.1. *List of studies that were considered technically out of scope or of borderline interest to decision problem*

Study	Company inclusion	EAC inclusion	Reasons
Carrara *et al*. 2010 [22]	✓	×	Manual exchange only
Webb *et al*. 2014	✓	×	Manual exchange only

[42]			
Billard *et al*. 2013 [43]	✓	✓	Procedural study evaluating the femoral approach (limited relevance).
Perseghin *et al*. 2013a [28]	✓	×	Mixed settings/indications (both Emergency and Elective) – cannot disaggregate data
Perseghin *et al*. 2013b [29]	✓	×	Mixed settings/indications (both Emergency and Elective) – cannot disaggregate data
Poullin *et al*. 2014 [30]	✓	×	No RBCx data (limited relevance)
Patel *et al*. 2013 [45]	✓	✓×	Device not stated (later clarified by company as Spectra Optia)
Tsitsikas *et al*. 2013 [46]	✓	✓×	Device not stated (later clarified by company as Spectra Optia)
Venkateswaran *et al*. 2011 [44]	✓	✓×	Device not stated (later clarified by company as Cobe Spectra)
Bahrani *et al*. 2011 [17]	×	✓	Within the scope and inclusion criteria
Anwar *et al*. 2010 [16]	×	✓	Within the scope and inclusion criteria

Figure 3.2**.** *PRISMA flow diagram showing studies assessed from the EAC's replication of the company's search strategy*



3.3.2 EAC's included and excluded studies

The EAC undertook an additional literature search (Section 3.1.1), which returned 2745 records (reduced to 1361 following de-duplication and removal of the search results from the replicated company search). The additional search was broader than the company's search, which resulted in a larger number of titles to sift. This aimed to identify any further articles that the company's search strategy may have missed.

The EAC filtered retrieved studies according to the criteria described in Table B1 of the company submission, with further clarification of elective and emergency apheresis indications specified by the British Committee for Standards in Haematology (BCSH) [25]. Filtering was performed first through reading the study title, and then through reading abstracts where necessary. If the study could not be excluded from examination of the abstract, the full text article was acquired.

During the hand-search of the annual conference abstracts for American Society for Apheresis, American Society of Haematology and British Society of Haematology, one abstract was identified by the EAC which had not been identified from the replication of the company's search strategy, but had been included by the Company in Table B3 of the clinical submission [32]. It is anticipated that the conference abstract by Trompeter *et al*. 2015 was originally identified by the company in the 18 records from additional sources (company submission, Figure 1).

Two additional articles met the EAC's selection criteria and were not identified by the company. These two conference abstracts were identified from the hand search of the annual conference abstracts described above. It is expected that these two abstracts were not identified by the company as they have recently been published and may not have been in the public domain at the time of their literature search. The remaining 1359 records were excluded due to the following reasons:

- Reviews
- Alternative studies on sickle cell disease and other haematological diseases
- Incorrect or unknown intervention
- Mixed indications where data could not be disaggregated
- Non-relevant outcomes

The EAC therefore included 34 unique studies, 30 of which were identified by both the company and EAC (Figure 3.2 PRISMA flow diagram), and 4 of which were additional studies which were identified by the EAC literature search. These studies are summarised in Table 3.2.

Table 3.2. *List of included studies identified by the EAC.*

Primary study reference	Population	Intervention	Comparator
Studies included by the company and EAC			
Cabibbo *et al*. 2005*	Adults and children with SCD at high risk for recurrent complications who had been hospitalised more than twice per year	RBCx (Cobe)	Manual exchange
Dedeken *et al*. 2014	Older children with SCD receiving chronic exchange, previously treated with manual exchange	RBCx (Spectra Optia)	Manual exchange
Duclos *et al*. 2013	Children with SCD treated by chronic RBCx	RBCx (Cobe)	Manual exchange
Fasano *et al*. 2015	Children with SCD on iron chelation and chronic transfusion (3-way comparison)	RBCx (Spectra Optia)	Manual exchange and TUT
Kaushal *et al*. 2013 (same data as Fasano *et al*. 2015)	Children with SCD on iron chelation and chronic transfusion (3-way comparison)	RBCx (Spectra Optia)	Manual exchange and TUT
Kuo *et al*. 2015	Adults with SCD and >1 RBCx over 1 year	RBCx (Spectra Optia)	Manual exchange
Kuo *et al*. 2012a (same data as Kuo *et al*. 2015)	Adults with SCD and >1 RBCx over 1 year	RBCx (Spectra Optia)	Manual exchange
Woods *et al*. 2014	Children and teens with SCD receiving regular RBCx for stroke prevention	RBCx (Spectra Optia)	Manual exchange
Baker *et al*. 2013	Paediatric patients with SCD	RBCx (Spectra Optia)	-
Kuo *et al*. 2012b	Adults with SCD	depl-RBCx (Spectra Optia)	RBCx (Spectra Optia)
Quirolo *et al*. 2015	Teens and Adults with SCD	depl-RBCx (Spectra Optia)	RBCx (Spectra Optia)
Quirolo *et al*.	Teens and Adults with SCD	depl-RBCx	RBCx (Spectra

2014 (same data as Quirolo *et al*. 2015)		(Spectra Optia)	Optia)
Sturgeon *et al*. 2009	Adults with SCD	RBCx (Spectra Optia)	No transfusion
Todd *et al*. 2015	Adults with SCD	RBCx (Spectra Optia)	-
Trompeter *et al*. 2015	Teens and adults with SCD receiving regular RBCx	depl-RBCx (Spectra Optia)	RBCx (Spectra Optia)
Asma *et al*. 2015	Pregnant women with SCD	RBCx (both)	No transfusion
Bavle *et al*. 2014	Children with SCD receiving RBCx for >1 year	RBCx (Cobe)	-
Billard *et al* 2013	Children with SCD	RBCx (Cobe)	-
Kalff *et al*. 2010	Adults with SCD	RBCx (Cobe)	-
Ma *et al*. 2005	Adults with SCD	IHD-RBCx (Cobe)	RBCx (Cobe)
Masera *et al*. 2007	Children with SCD at high risk for vaso-occlusive complications	RBCx (Cobe)	-
Sarode *et al*. 2011	Adults with SCA, stable with history of thrombotic stroke	IHD-RBCx (Cobe)	RBCx (Cobe)
Shrestha *et al*. 2015	Adults with SCD on scheduled RBCx	RBCx (Cobe)	-
Willis *et al*. 2011	Young adults with SCD having monthly RBCx	RBCx (Cobe)	-
Poullin *et al*. (2014)	Adults with SCD	RBCx (Spectra Optia)	RBCx (Cobe)
Turhan *et al*. 2013	Patients with SCD	RBCx (Spectra Optia)	RBCx (Cobe)
Adams *et al*. 1996	Children and teens with SCD	RBCx (Cobe)	TUT
Hilliard *et al*. 1998	Teens and adults with SCD and history of stroke converted from simple transfusion to auto RBCx	RBCx (Cobe)	TUT
Singer *et al*. 1999	Children with SCD	RBCx (Cobe)	TUT
Wahl *et al*. 2012	Paediatric patients on chronic transfusions for SCD	RBCx (Cobe)	Simple transfusion
Additional studies included by the EAC			
Bahrani *et al*. 2011	Patients with SCD	RBCx (Spectra Optia)	-

Anwar *et al*. 2010	Patients with SCD	depl-RBCx (Spectra Optia)	RBCx (Spectra Optia)
Anwar *et al*. 2015	Patients with SCD	depl-RBCx (Spectra Optia)	RBCx (Spectra Optia)
Kinney *et al*. 2015	Patients with SCD	RBCx (Optia)	RBCx (Cobe)
*Study references underlined indicate peer-reviewed studies			

3.4 Overview of methodologies of all included studies

The studies included by the company in table B3 of the submission as relevant published evidence on the Spectra Optia and its predecessor, the Cobe Spectra system, are generally of low quality and results are subject to a high degree of bias and uncertainty. This makes interpretation of results and conclusions difficult, particularly when generalising to the NHS.

Of the studies included, six were described by the company as comparative studies between automated RBCx (two on Cobe Spectra [2, 4], four on Spectra Optia [3, 5-7]) and manual RBCx. However, none of these six studies were prospectively designed experimental comparative studies; all were retrospective observational studies using routinely available data on the intervention and its comparator. In addition, most of the studies on the Spectra Optia system were reported as abstracts and/or were not peer reviewed. This limits their validity and makes critical appraisal difficult. Nevertheless, these studies represent the only comparative evidence for the Spectra Optia system and consequently were reviewed by the EAC in detail (full independent critical appraisal).

Other studies included were single-armed investigations of manual exchange [22, 42], the Spectra Optia system [11, 47-51], and the Cobe Spectra system [8-10, 12, 13, 20, 38, 43]. These studies may be used to support the absolute outcomes reported in individual arms of the comparative studies, but used alone provide no information on the comparative effectiveness of automated and manual RBCx due to the heterogeneity of the populations. Many of these studies were reported in abstract form only; for these studies the EAC has opted to review the company's critical appraisal only and examine specific outcomes of these studies in more detail when they form an important part of the company submission or claims. The EAC has performed a more thorough critical appraisal of some of the more relevant studies published in full in peer reviewed journals. An example of this is the study by Quirolo *et al.* (2015) [11], which although single armed, was prospective and considered to be of higher quality than some of the comparative studies.

The company also included studies comparing the Spectra Optia system with the Cobe Spectra system [28, 30, 31]. These were primarily included to support the inclusion of evidence on the Cobe Spectra system as an intervention (and thus inclusion of comparative and single armed studies of Cobe Spectra, see Section 2.3). The EAC considers these studies were of poor methodological quality and did not add much to the evidence base, and has briefly reviewed them.

The company also included studies comparing automated RBCx (one with Spectra Optia [5] and three with Cobe Spectra [21, 23, 52]) with simple top up transfusions. As discussed in Section 2.3.4, the EAC did not consider that top up transfusion was a valid comparator and, in any case, did not consider these studies added substantially to the evidence base. These studies are therefore only described briefly.

Finally, one study was included that compared the use of automated RBCx (Spectra Optia and Cobe Spectra) with no treatment in pregnant women with SCD [19]. This study is briefly described. However, the evidence for the use of Cobe Spectra in subgroups is also described more fully in Section 3.6.5.

The characteristics of the six comparative studies are summarised in Table 3.3. Note: to avoid confusion, where multiple references are provided for the same study, the EAC has referenced the paper that it considered was reported more clearly or completely, or the latest version of the study. The characteristics of the remaining studies included by the company that were considered in scope are described in Table 3.4.

Four additional studies were presented by the company in tables B10a-d of their submission as a studies solely relating to adverse events [41, 44-46]. Only one of these stated that the device used was Cobe Spectra [41], the other three were not identified by the EAC literature sift, since the intervention was not explicitly stated.

Table 3.3. *Characteristics of the six comparative studies.*

Study author	**Study design and publication type**	**Patients, procedures and setting**	**Intervention**	**Comparator**
Cabibbo *et al.* (2005) [2]	Retrospective observational study. Full article in peer reviewed journal.	20 patients (mixed age) 394 procedures Italy	Baxter CS300+ system Haemonetics MCS+ system Cobe Spectra	Manual RBCx
Dedeken *et al.* (2014) [3]	Retrospective 'before and after' study Conference abstract	10 older children Total number of procedures unclear (181 reported but unclear what it is referring to) Belgium	Spectra Optia (following manual RBCx)	Manual RBCx (before RBCx)
Duclos *et al.* (2013) [4]	Retrospective matched case series. Full article in peer reviewed journal.	10 older children 184 Procedures France	Cobe Spectra (for chronic SCD)	Manual RBCx (for RBCx)
Fasano *et al.* (2015) [5]	Retrospective observational study.	36 patients Minimum 6 month data collection (procedure number	Not stated but thought to be Spectra Optia	Simple ('top up') transfusion Partial exchange transfusion

Study author	Study design and publication type	Patients, procedures and setting	Intervention	Comparator
	Conference abstract.	unknown) United States		
Kuo *et al* (2015) [6]	Retrospective observational cohort study. Published in journal (probably not peer reviewed)	51 patients 401 procedures United Kingdom	Spectra Optia	Manual RBCx
Woods *et al.* (2014) [7]	Retrospective observational study Conference abstract	38 patients Procedure number not reported United States.	Not stated but thought to be Spectra Optia	Manual exchange (but some mixed)

Table 3.4. *Characteristics of non-comparative studies (studies considered to be in scope only).*

Submission and assessment report sections	Study author	Study design and publication type	Patients, procedures and setting	Intervention	Comparator
Spectra Optia only (Section 3.4.4)	Baker *et al.* (2013) [47]	Retrospective case series Conference abstract	6 patients Canada	Spectra Optia standard exchange	None
	Kuo *et al.* (2012) [48]	Retrospective observational study Conference abstract	7 patients 135 procedures Canada	Spectra Optia standard exchange	Spectra Optia depletion exchange
	Quirolo *et al.* (2015) [11]	Prospective observational study (single armed) Peer-reviewed journal	72 patients/procedures (safety) 60 patients/procedures (efficacy) United States	Spectra Optia.	Depletion exchange Spectra Optia (subgroup analysis)

Submission and assessment report sections	Study author	Study design and publication type	Patients, procedures and setting	Intervention	Comparator
	Sturgeon *et al.* (2009) [49]	Retrospective observational study Conference abstract	74 patients 1578 procedures Canada	Spectra Optia standard exchange	Subgroup analysis of RBCx regimen frequency
	Todd *et al.* (2015) [50]	Retrospective observational study Conference abstract	50 patients Mean procedures = 8 United Kingdom	Spectra Optia standard exchange	None
	Trompeter *et al.* (2015) [51]	Retrospective observational study Conference abstract	70 patients United Kingdom	Spectra Optia standard exchange	Spectra Optia depletion exchange

Submission and assessment report sections	Study author	Study design and publication type	Patients, procedures and setting	Intervention	Comparator
RBCx in pregnancy (Section 3.4.5)	Asma *et al.* (2015) [19]	Retrospective observational study Study in peer-reviewed journal	37 pregnant women 43 procedures Turkey	Spectra Optia and Cobe Spectra systems (24 patients)	No transfusions (13 patients)
Cobe Spectra only (Section 3.4.6)	Bavle *et al.* (2014) [8]	Retrospective observational study, matched controls Full article in peer-reviewed journal	35 children United States	Cobe Spectra system	64 matched controls
	Billard et al. (2013) [43]	Retrospective case series Full article in peer-reviewed journal	18 children 443 procedures France	Cobe Spectra system	None
	Kalff *et al.* (2010)	Retrospective case	13 patients	Cobe Spectra system	None

Submission and assessment report sections	Study author	Study design and publication type	Patients, procedures and setting	Intervention	Comparator
	[9]	series Full article in peer reviewed journal	Australia		
	Ma *et al.* (2005) [38]	Retrospective observational study Conference abstract	7 patients 77 procedures United States	Cobe Spectra standard exchange	Cobe Spectra isovolaemic haemodilution exchange
	Masera *et al.* (2007) [10]	Retrospective data review Full article in peer-reviewed journal	34 patients Italy	Cobe Spectra system	None
	Sarode *et al.* (2011) [12]	Retrospective observational study with historical controls Full article in peer-reviewed journal	20 patients United States	Cobe Spectra isovolaemic haemodilution exchange	6 historical controls (standard Cobe Spectra exchange)

Submission and assessment report sections	Study author	Study design and publication type	Patients, procedures and setting	Intervention	Comparator
	Shrestha *et al.* (2015) [13]	Retrospective observational study Full article in peer reviewed journal	29 patients 318 procedures United States	Cobe Spectra system	None
	Willis *et al.* (2011) [20]	Retrospective case series Conference abstract	5 patients 63 procedures United States	Cobe Spectra system	None
Spectra Optia versus Cobe Spectra systems (Section 3.4.7)	Poullin *et al.* [30]	Retrospective observational study Conference abstract	23 patients on chronic transfusion exchange therapy 46 chronic procedures in 23 patients France	Spectra Optia depletion-exchange	Cobe Spectra isovolaemic haemodilution exchange

Submission and assessment report sections	Study author	Study design and publication type	Patients, procedures and setting	Intervention	Comparator
	Turhan *et al.* (2013) [31]	Retrospective observational study	132 patients 347 procedures Turkey	Spectra Optia system	Cobe Spectra system

3.5 Overview and critique of the company's critical appraisal

3.5.1 Studies comparing manual with automated RBCx

As discussed, six studies were identified that compared automated RBCx with manual RBCx, as specified in the scope. The EAC considered that the company had provided an adequate appraisal of these studies in tabular format (Tables B8a-f and B8k). These critical appraisal tables are generally designed for prospective cohort studies of higher quality than the comparative studies reported. The EAC has drawn attention to any element of these tables they disagreed with or considered had been omitted. However, the company did not provide a detailed narrative for these key studies, which the EAC will now also provide. A summary table of the quality of these studies is reported in Table 3.5.

Cabibbo *et al.* (2005)

The company did not complete a full critical appraisal table for the study by Cabibbo *et al.* (2015) [2] because it was considered to be too poorly reported (Table B8a of company submission). The EAC would agree with this assertion and agrees with the comments stated by the company.

This was a probably a retrospective observational study (study type not stated) as it did not require ethical approval, and was reported in full in a peer reviewed journal. In the study, 20 patients were recruited who had received manual or automated RCBX for a variety of clinical indications, most of which appeared to be emergency situations, at least in the first instance (which may place the study out of scope). In total, 206 automated RBCx procedures were reported in 13 patients which were provided by either the Cobe Spectra system (60/206), the Baxter CS300+ system (68/206), or the Haemonetics MCS+ system (78/206). It was not possible to disaggregate the effects of these systems (which may place it out of scope). Manual exchange was performed in 7 patients (188 procedures). However, these patients received manual rather than automated exchange because of poor compliance or difficult venous access, which is a major confounder and source of selection bias. The baseline characteristics of the two groups appear to be different, with median age in the automated cohort being 32 years compared with 11 years for manual (similarly median weight was 70 Kg compared with 20 Kg), so there are grounds for concern that the groups were not comparable.

The aims of this study were not clear and results may have been reported selectively (reporting bias). The results reported procedure time, RBC units used, clinical improvement, iron overload, and HbS <30% achieved. However,

it was not possible to determine when these outcomes were measured or how they compared to baseline results. No statistical analysis was reported. In Table 2 of the study, procedure times are reported but no distributional data is offered, so it is not possible to determine if there is a statistical difference.

In conclusion, this was a poorly designed and analysed study which was inadequately reported. It does not offer an objective comparison between the apheresis methods because the groups are different. In addition, it is not possible to determine the outcomes relative to baseline or disaggregate the effects of the different automated apheresis methods. The EAC therefore would consider any data from this trial to be treated with caution.

Dedeken *et al.* (2014)

The study by Dedeken *et al.* (2014) [3] was published as a conference abstract that was not peer reviewed, so cannot be fully appraised. The company critically appraised this study using a full table (Table B7b); the EAC did not disagree with the content of this table.

This was a retrospective observational study in which ten older children (median age 11.8 years) who were receiving manual RBCx (median 1.9 years duration) were switched to automated RBCx (Spectra Optia, median 1.7 years). It was unclear how many procedures were reported in each group. In Table B6b the company had described this as an "observational case-crossover" but this is probably not true in the normal sense of this definition; instead the EAC would refer to this as a 'before and after' study; this type of study is subject to significant confounding.

Patients were recruited for Spectra Optia only if they were eligible, which included "sufficient venous access", thus they were highly selected. Outcomes included HbS%, ferritin (µg/L), duration of procedure, and interval between procedures. Costs were also reported but the methodology and data sources used were not transparent. The authors use Friedman's test and Dunn's Multiple Comparison test, but it is unclear to the EAC why these relatively obscure tests (which apply to ranked data) were applied to continuous data, and the results of the analysis might therefore be misleading.

In conclusion, the EAC considered that this was a poorly reported paper and it was not possible to fully interpret the methodology used in the 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. This was not a true comparative study and the reported results could not be disaggregated. In addition, the number of patients recruited was low

and the number of procedures unclear. For these reasons, the EAC would consider that any data obtained from this study be treated with caution.

Duclos *et al.* (2013)

The study by Duclos *et al.* (2013) [4] was published as a full article in a peer reviewed journal. The company critically appraised this study using a full table (Table B7c); the EAC did not disagree with the content of this table.

This was a retrospective case-matched study in which 5 children (average age 12 years) from different treating centres were treated for chronic SCD 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 received manual RBCx (124 procedures), and results between the two centres were compared.

The primary outcome of the study appeared to be comparative measurement of HbS% levels, although it is not clear if any outcomes were predetermined before analysis. In the event, only pre-procedure levels were fully available so these were used to act as a proxy measurement. Other clinical, technical, and resource use outcomes were also included. Statistical analysis was performed using the Mann Whitney U and t tests for continuous variables which would be appropriate if applied correctly (non-normal and normal distributions). However, as the company indicated, a reported relationship between HbS% levels and procedure interval was not accompanied with appropriate statistical analysis.

There were several potential sources of bias which were discussed by both the paper's authors and the company. Most importantly was the confounding factor that the cohorts were treated in different centres who may have had different treatment regimens and physician practices, including treatments other than RBCx. Other sources of bias include selection bias (minimised but not eliminated by matching) and reporting bias. This study was also small, encompassing only ten individuals. However, overall this was a relatively well conducted and reported study that provides insight into the use of the Cobe Spectra system (and by extension, the Spectra Optia system) in older children.

Fasano *et al.* (2015)

The study by Fasano *et al.* (2015) [5] was published as a conference abstract that was not peer reviewed, so cannot be fully appraised. The company critically appraised this study using a full table (Table B7d); the EAC did not disagree with the content of this table.

This was a retrospective observational study whose explicit aim was to compare different procedures efficacy in reducing ferritin and liver iron content. Three procedures were used; these were simple transfusion (20 patients), partial transfusion (details of procedure not reported, 6 patients), and automated RBCx (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 the number of procedures retrieved was not reported and it is possible data was missing. It is implied, but not stated, that patients received separate therapies, but it is not clear if some overlap between treatment arms may be present. All patients were on chelation therapy during the study (i.e. already in iron overload); this is a subgroup stated in the scope.

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. Where data allowed (22 patients, cohorts not specified), the Kruskal Wallis test was used to determine differences in liver iron content. This would be appropriate if the data was non-normally distributed.

In summary, this study was poorly reported to the extent it was not possible to fully understand how it was conducted. The population enrolled 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 comparators included the use of top up transfusion which the EAC regards as out of scope. Additionally, the method of partial exchange was not described and is not directly comparable to automated RBCx; full manual exchange was not investigated. As reported, this study cannot be considered to be a true comparative study in the scope of the decision problem and so results from it should be treated with caution.

Kuo *et al.* (2015)

The study by Kuo *et al.* (2015) [6] was published as correspondence (letter to editor) in a journal; it is unclear if this was peer reviewed or not but it is likely it was not. The company critically appraised this study using a full table (Table B7e); the EAC did not disagree with the content of this table.

This was the only comparative study that was set in the UK (Bart's Health Trust and Guy's and St. Thomas NHS trust). The aim of the study was to investigate "whether adult SCD patients on manual RBCx differ from those on automated RBCx in their ability to achieve pre-defined haematological targets, rate of complications, blood usage and clinical outcomes over a 1-year period".

This study was described as a retrospective cohort study that did not report the need for ethical approval. The study investigated one cohort who received Spectra Optia for chronic SCD in one centre, and another cohort who received manual RBCx. In total 51 subjects were enrolled who received 401 procedures, although no details of enrolment were stated (e.g. consecutive or total recruitment). 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 receiving manual RBCx were significantly younger (median 23 years) compared with those receiving Spectra Optia RBCx (31 years, p=0.035). Also significantly more patients receiving manual RBCx were administered the procedure through the peripheral venous route rather than central routes (p<0.0001).

The outcomes reported in the study included pre-procedure HbS% ("pre-RBCx HbS/SC fraction"), but did not report post-procedure HbS%. Instead, the main outcome reported was the proportion of sessions where the target HbS% was met. The threshold for this outcome was set at 2/3 sessions meeting the target; the reasons for this seemingly arbitrary threshold are unclear. This data was used to calculate odds ratios using the Mantel-Haenszel method. Other outcomes included achieving haematocrit target, resource use (packed RBC utilisation, procedure time, and procedure intervals), and adverse effects.

The strengths of this study were that it was a head to head comparison of methods with a reasonably high number of enrolled patients and procedures. The study was also relatively well reported and presented. However, a weakness of the study was that it was performed in two separate hospitals and therefore subject to the same 'centre effect' as described by Duclos *et al.* (2013) [4]. The authors acknowledge the confounding nature of the design, which is always present with retrospective studies, as well as the potential for selection bias. Indeed, there was strong evidence the patients treated were not equivalent, particularly regarding age. 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. However, 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)

The study by Woods *et al.* (2014) [7] was published as a conference abstract that was not peer reviewed, so cannot be fully appraised. The company critically appraised this study using a full table (Table B7f); the EAC did not disagree with the content of this table.

This was described as a retrospective observational study of 38 patients in a single institution which included data over a 2 year period. The number of procedures was not reported, but in the first year 5 received automated RBCx (presumed Spectra Optia, as stated by company), 17 received manual RBCx, and 16 received both procedures. In the second year, 13 received Spectra Optia and 25 received manual RBCx, but results for this year were not presented separately and thus treatments cannot be disaggregated. Patients were actively selected for Spectra Optia on the basis of age and size, and could choose not to receive Spectra Optia.

Outcomes reported in the study in the study included duration and mode of transfusion therapy, achievement of HbS% targets, ferritin levels, and catheter complications. However, these were difficult to interpret because baseline values, number of procedures, and time of outcome were not reported. The authors stated they used Fisher's exact test and Mann-Whitney U test for statistical analysis. This would have been appropriate for small numbers.

In summary, 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. Therefore the EAC considers results from this study should be treated with caution.

3.5.2 Summary of quality of comparative studies

The key comparative studies were all retrospective observational studies of various analytical designs. Although the studies were described by the company as comparative, they did not have experimental designs and any comparison made is likely to be subject to a high degree of confounding and bias. In some cases, the populations were poorly described or mixed. In other cases, it was clear that the populations selected for automated and manual RBCx were different (typically in age). This, together with the fact some studies mixed treatments, means it is very difficult to ascribe an effect or outcome to the specific system under study.

The company rightly states in section 7.9.2 that retrospective studies which use routine data are at low risk of performance and assessment bias. However, it is also true that these studies can only use the data that has been recorded, and therefore there is a reliance on this data of being of usable quality and relevance. Whilst many of the outcomes reported in these studies may be considered as 'hard' physiological endpoints recorded in routine data, the possibility of transcription errors (through the operator or investigator)

should also be considered. The company rightly points out that retrospective studies are subject to selection bias or, as described above, different populations may be indicated for the intervention and comparator. Another issue which the company did not address is that of reporting bias, whereby only selected outcomes are reported [53]. This may be particularly problematic with retrospective studies where outcomes are often not pre-determined.

The EAC has summarised the quality of the six comparative studies, in terms of method, reporting, potential for confounding, potential for bias, and overall usefulness for the decision problem, in Table 3.5. Note that adjectives describing these studies are *relative* to the overall evidence base for the Cobe Spectra and Spectra Optia systems; all of these studies would be regarded as low quality evidence using standard evidence grading systems [54].

Table 3.5 *Quality assessment of comparative papers*.

Study author	Method quality	Reporting quality	Potential for confounding and bias	Overall uncertainty
Cabibbo *et al.* (2005) [2]	Very poor. Unclear objectives and no structured method.	Very poor. Unable to fully interpret results or method.	Very high. Patient selection and mixed treatment regimens particular issues.	Very high. Unable to attribute outcomes to the Cobe Spectra system.
Dedeken *et al.* (2014) [3]	Poor. 'Before and after' study not truly comparative.	Poor. Reporting limited to abstract.	High. All patients received manual RBCx first.	High. Results should be treated with caution.
Duclos *et al.* (2013) [4]	Good. Case-matched study using appropriate methodology.	Good. Full published paper. Well described and easy to interpret.	Medium Arms treated in separate centres.	Medium. Low patient numbers adds to residual uncertainty.
Fasano *et al.* (2015) [5]	Poor. A lack of detail to determine how the study was	Poor. Restricted to abstract format.	Very high. Patient selection and possible use of mixed	Very high. Comparators not equivalent to standard manual RBCx

Study author	Method quality	Reporting quality	Potential for confounding and bias	Overall uncertainty
	undertaken.		treatments.	(possibly out of scope).
Kuo *et al.* (2015) [6]	Good. Comparison between two similar centres.	Medium. Published more completely than conference abstract, but probably not peer-reviewed.	High. Cohorts were not equivalent at baseline.	Medium. Provides useful UK-relevant data on the Spectra Optia system.
Woods *et al* (2014) [7]	Poor. Study cohorts not clearly distinct.	Poor. Restricted to abstract format.	High. Patient selection, mixed treatments.	High.

3.5.3 Studies on manual RBCx only

The two studies identified by the company appear to have been incidental findings and are not discussed further because they are not in the scope of the decision problem (see section 3.3) as they did not include the technology of interest, Spectra Optia (or Cobe Spectra). As no specific search strategy was reported for the identification of studies on manual RBCx (which would be expected to identify a large number of studies), there is a concern that these studies could have been cherry picked, or that other studies were excluded on the basis of results.

These studies have been critically appraised by the company in Tables B8g and h (abridged). The study by Carrara *et al.* (2010) [22] was a conference abstract which reported descriptive rather than analytical results; hence the usefulness of this study (in putting manual RBCx in context) is limited. The study by Webb *et al.* (2014) [42] was also reported as a conference abstract. It described a retrospective case series of 15 children receiving manual transfusions for SCD, and because of the small participant number and poor reporting conclusions are limited. Nevertheless, this study was used to estimate important parameters in the economic section of the submission (Section 4.2.4).

3.5.4 Studies on Spectra Optia only (single arm)

Quirolo *et al*. (2015)

The study by Quirolo *et al.* (2015) [11] was published in a peer-reviewed journal. Although not described as a comparative study by the company, the EAC has highlighted this study for particular attention because it is one of the only prospective studies available, and it did make some within-cohort comparisons. The EAC has been informed this study was instrumental in the Spectra Optia system receiving FDA (Food and Drugs Administration) 510(k) approval for treatment of SCD (see EAC Correspondence Log). The company critically appraised this study using a full table (Table B7k); the EAC did not disagree with the content of this table. This was a prospective multi-centre study that had been registered in clinicaltrials.gov (NCT 01736657) with predefined primary and secondary endpoints [55]. Eligible and consenting patients (over 12 years age) were enrolled to receive either standard RBCx or depletion exchange with Spectra Optia. The modality was chosen at the discretion of the investigator and thus was subject to considerable selection bias. In total, 72 patients were enrolled in the study, although only 60 of these were evaluated for efficacy (potentially a source of bias). Only one procedure was reported per patient.

The pre-specified primary endpoint of the Quirolo study was the ability of the Spectra Optia to accurately achieve targets on the fraction of a patient's original red cells remaining (FCR). Secondary endpoints included the systems 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 dichotomous (yes/no) endpoints. Subgroup analysis of patients who received standard RBCx (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; nor was the rationale for the acceptable range for the primary outcome.

The strength of the Quirolo study was that it was prospective with predefined primary and secondary endpoints, was well reported and is of greater methodological quality than most of the studies of this system. But it was subject to potential bias in terms of patient selection and assessment bias for the subjective (secondary) outcomes. The study did not attempt to control for confounding variables. Nevertheless, this study provides good evidence for the short-term efficacy and safety of Spectra Optia. The baseline characteristics of the subgroups 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.

Non-peer reviewed studies

The study by Baker *et al.* (2013) [47] was reported as a conference abstract. The company critically appraised this study using a full table (Table B7i); the EAC did not disagree with the content of this table. This was a descriptive study on the use of the Cobe Spectra system, and did not appear have any specific aims or pre-defined outcomes. It is unclear how patients were selected. The EAC notes that target post-procedure HbS% levels in this institution (10%) were lower than usually practised in the UK (30 to 50%) [26]. Due to the presence of confounding and bias, the EAC recommends that data arising from this study are treated with caution.

The study by Kuo *et al.* (2012) was reported as a conference abstract. The company critically appraised this paper using an abridged table (Table B7j); the EAC agrees with the content of this table. This was a 'before and after' study that aimed to compare standard RBCx with Spectra Optia with depletion exchange. Comparisons were made on a "patient by patient" basis, but baseline data were not reported making interpretation difficult. The method of patient selection was not described, and methods of statistical analysis were

also not reported. There was some evidence of possible reporting bias in the results, with multiple outcomes analysed and mainly 'significant' results being reported. Due to the poor quality of reporting and potential for bias the EAC recommends that data arising from this study should be treated with caution.

The study by Sturgeon *et al.* (2009) [49] was a retrospective design reported as a conference abstract. The company critically appraised this study using a full table (Table B7l); the EAC did not disagree with the content of this table. Patients were divided into 4 groups (total patients n = 74, 1578 exchange procedures) depending on the frequency of the RBCx regimen. The primary outcomes were haemoglobin and serum ferritin levels and the relationship between this and regimen frequency. Patient selection and statistical methods were not described. The EAC recommends that results from this study be treated with caution due to the limited reporting and lack of peer review.

The study by Todd *et al.* (2015) [50] was reported as a conference abstract and described as a retrospective study. The company did not fully critically appraise this paper (Table B7m). Fifty patients were selected (method not stated) and the mean average number of procedures was eight (total number of procedures not reported). Methods of statistical analysis were not described. The EAC recommends that results from this study be treated with caution due to the limited reporting and lack of peer review.

The study by Trompeter *et al.* (2015) [51] was reported as a conference abstract and described as a retrospective study. The company did not fully critically appraise this paper (Table B7n). The device name was not explicitly named, but the company stated that the hospital where the study was conducted use the Spectra Optia system. Seventy patients were included in the study but the number of procedures was not reported. This study was a presented as a narrative and did not report numerical values. Therefore its value in answering the decision problem is limited.

3.5.5 Studies in pregnant women

One study was identified by the company that investigated the use of RBCx (Cobe Spectra and Spectra Optia systems) in pregnant women. This was the study by Asma *et al.* (2015) [19]. It was published in a peer-reviewed journal and is critically appraised by the company in Table B8o; the EAC did not disagree with this appraisal.

This was a single centre retrospective study which focussed on the use of RBCx for the treatment of painful crises during pregnancy. In total 37 women were included in the study (selection method not described), and of these 24 received RBCx (total 43 procedures) and 13 received no exchange treatment. Technically, these patients are out of scope, making this in effect a single-

armed (before and after) study. The main outcomes reported were technical parameters, complications, and maternal death. The statistical analysis described appeared to be appropriate.

The EAC considered that this study reported useful data that was however somewhat peripheral to the scope of the decision problem. Caution should be used when interpreting the results due to the lack of appropriate comparator data and the potential for confounding and selection bias.

3.5.6 Studies on Cobe Spectra only (single arm)

Bavle *et al*. (2014)

The study by Bavle *et al.* (2014) [8] was published as a full article in a peer-reviewed journal and was critically appraised by the company in Table B8p (abridged).

This was a retrospective analysis of the growth of children with sickle cell disease who received regular RBCx. They compared the height, weight and BMI of 36 patients on long term RBCx (LTE) with their own growth prior to LTE initiation and with two control groups, all patients with sickle cell disease from the Cooperative Study of Sickle Cell Disease (CSSCD) and a sub-set of 64 matched controls taken from CSSCD.

The study subjects showed a statistically significant increase in height, weight and BMI, compared to those prior to LTE initiation ($p \leq 0.0001$). They found a statistically significant improvement in the weight, height, and BMI of the study subjects compared with the matched controls from the CSSCD and the entire paediatric CSSCD cohort ($p<0.01$). Patients who had not been on regular simple transfusions prior to starting LTE (33/36) also had a mean serum ferritin of 681 ng/ml after LTE for an average duration of 63 months.

The EAC agreed with the company's interpretation of this study. 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 CSSD dataset for every subject; although, only 1 matched control was found for 8 of the study subjects. However, a Wald test under the framework of linear mixed effect models was used to ensure there were no statistically different growth parameters for the study subjects and matched controls. The authors used z-score curves for the growth parameters which allowed for comparability across ages and sexes.

Billard *et al*. (2013)

The study by Billard et al, (2013) [43] was published as a full article in a peer-reviewed journal and was critically appraised by the company in Table B8q.

This was a small retrospective case series with the primary aim of describing the treatment of 18 children (443 procedures) who received RBCx with the Cobe Spectra system with venous access implemented through a short term-indwelling double-lumen catheter. Follow up was over a 6.5 year period and patients were enrolled consecutively.

Whilst this study was relatively well described, it was a descriptive case series, with most results described on an individual patient basis only; these included mean pre- and post procedural HbS(%) and ferritin levels before and after the treatment period (tested with Wilcoxon signed rank test). This limited before and after analysis was subject to confounding and bias. As no comparator (historical or otherwise) was used, it was difficult to place the results of this study in context or address the primary aim of the study, which was to determine the efficacy and safety of the indwelling catheter.

Kalff *et al*. (2010)

The study by Kalff *et al.* (2010) [9] was published as a full article in a peer-reviewed journal and was critically appraised by the company in Table B8r (abridged).

This was a retrospective case series of patients from one centre who received RBCx using the Cobe Spectra System. The study included 13 adult patients and evaluated the effectiveness of a regular RBCx programme. Patients were exchanged via peripheral venous cannulae or arterio-venous fistula, generally at an initial frequency of 4 weeks and subsequently at 4-6 week intervals. End-points included 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.

The regular RBCx programme reduced HbS levels to the target of <30% immediately post-exchange in all except 2 patients. A total of 16 acute sickle-related events occurred in 5 patients in 846 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 were maintained in patients with normal baseline levels and reduced in those in those with slightly higher baseline levels without chelation therapy.

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). Due to the retrospective nature of this study, 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 no baseline information. For this reason they were unable to demonstrate significant before/after comparisons for the main outcome measures.

Masera *et al*. (2007)

The study by Masera *et al.* (2007) [10] was reported as a full article in a peer-reviewed journal, and was critically appraised by the company (Table B8t, abridged).

This was an 11 year retrospective review of routine data from a cohort of 34 patients with sickle cell disease treated in one hospital. The authors focussed on 13 high-risk patients and reported efficacy, safety and cost outcomes of a periodic regimen of erythroexchange with Cobe Spectra. Outcomes included change in HbS and ferritin levels, hospital admissions and painful crises. The authors reported a reduction in HbS and ferritin levels, hospital admissions and painful crises, when compared with data prior to commencement of erythroexchange, but the reported changes were not tested for significance.

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. However, the combined treatment of periodic erythroexchange with hydroxyurea does provide a new approach to be considered for patients with the most severe and complicated of situations. The study was relatively poorly reported and for this reason, the EAC recommends that data taken from this study is used with caution.

Sarode *et al*. (2011)

The study by Sarode *et al.* (2011) [12] was published as a full article in a peer-reviewed journal. It has been critically appraised by the company in Table B8u.

This study is a retrospective review of a two-phase automated RBCX method (IHD-RBCX) using isovolaemic haemodilution with conventional red blood cell exchange (C-RBCX) in comparison to the C-RBCX protocol alone. Fourteen patients receiving IHD-RBCX (using the Cobe Spectra device) were compared with 6 historical controls receiving C-RBCX, and outcomes focussed on resource use. The authors reported an increase in the

haematocrit and a decrease in HbS following the IHD-RBCX procedure; however, these changes were not tested for statistical significance. They also report that IHD-RBCX used a significantly lower volume of packed RBC than for C-RBCX. Overall procedures were reviewed for rate of adverse events and were higher in the IHD-RBCX group than in the C-RBCX group.

The EAC would recommend caution in interpreting results from this study due to potential 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. Also, given the chronic nature of sickle cell disease, the inter-procedure intervals in a given patient could be affected by a variety of factors, including pregnancy, infections and illnesses. Additionally, it describes a comparison between two modes for the Cobe Spectra system which is not directly relevant to the scope.

Shrestha *et al*. (2015)

The study by Shrestha *et al.* (2015) [13] was published as a full article in a peer-reviewed journal and has been fairly critically appraised by the company (Table B8v).

This was a retrospective observational cohort study that was designed to compare two methods of vascular access (dual lumen port valves with temporary central venous and peripheral catheters) during automated exchange with the Cobe Spectra system. They reported outcomes including inlet speed, duration of procedures and rates of complications. Twenty-nine adults with sickle cell disease who underwent a total of 318 procedures were included for analysis. The authors reported a mean duration of 2 hours for the red blood cell exchange 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 Haemoglobin targets, respectively.

The EAC would recommend caution in interpreting results from this study on the efficacy of Cobe Spectra because it was designed to compare two types of venous access. Specifically, the selection of patients is not reported which opens up the potential for selection bias. The procedures for data collection were similarly not reported. Finally, the outcome measures were not directly relevant to the scope

Non-peer reviewed studies

The study by Ma *et al*., (2005) [38] was presented as a conference abstract and was critically appraised by the company in Table B8s (abridged). This was a retrospective observational study of 7 patients receiving 77 RBCx

procedures, and aimed to compare standard exchange with isovolaemic haemodilution with the Cobe Spectra device (equivalent to depletion exchange on the Spectra Optia device). They reported that post red blood cell exchange, the haemoglobin levels were within 5% of the targeted goal in 95% of procedures. The isovolemic haemodilution also provided a mean savings of 2.9 mL pRBC/kg body weight.

Due to this study being reported as a conference abstract, little information was provided and the study was poorly reported. Patient selection and data collection is similarly not reported, and one patient was excluded from the analysis due to a post-haemodilution haematocrit of 32% (target <24%). The study is potentially subject to confounding and performance and assessment bias; results therefore should be treated with caution.

The study by Willis *et al.* (2011) [20] was published as a conference abstract and has been critically appraised by the company (Table B8w, abridged). This was a case series of five patients receiving chronic RBCx with the Cobe Spectra system. The 5 patients were exchanged monthly for stroke prophylaxis and the primary outcome was ferritin levels and “many” patients were receiving concomitant chelation therapy. The authors primarily followed the reduction in RbS, but only reported an average decrease in ferritin levels of 45.8% following chronic RBCx. Only 1 out of the 5 patients did not require concomitant chelation therapy.

Due to this study being reported as a conference abstract, little information was provided and the study was poorly reported. As this was described as an ‘experience’ with 5 patients, the clinical data was likely to be routinely collected. Therefore, the study is potentially subject to confounding and selection, performance and assessment bias, and results should be treated with caution.

3.5.7 Studies comparing the Spectra Optia and Cobe Spectra systems

The company included three papers which they claimed supported the equivalence of the Spectra Optia and Cobe Spectra systems. The EAC has accepted the systems have equivalent efficacy, with the Spectra Optia having additional safety and operational features. These studies are briefly described in this section.

Persghin *et al*. (2013)

The study by Perseghin *et al.* (2013) [29] was published as a full article in a peer-reviewed journal, and was critically appraised in by the company in Table B8x; the EAC does not disagree with the content of this table. This was a retrospective study of adults and children receiving the Spectra Optia

system (15 patients, 25 procedures) compared with the Cobe Spectra system (12 patients, 21 procedures) as a historical control. However, some patients received both treatments meaning the arms were not truly independent. Additionally, four procedures in the Cobe Spectra arm and nine in the Spectra Optia were emergency procedures. Since there was no attempt to disaggregate these procedures, technically this paper was out of scope.

Non-peer reviewed studies

The study by Poullin *et al.* [30] was presented as a conference abstract and critically appraised by the company in Table B8y. This was a retrospective observational study comparing depletion-exchange on the Spectra Optia system with a modified isovolaemic haemodilution protocol on the Cobe Spectra system. In total 327 procedures were performed in 43 patients, with the authors stating that each patient received treatment from both systems and acted as their own control. However, it is not clear from the report how this was achieved. Emergency procedures were also included in the study, but separate results were reported for 46 chronic transfusion exchanges in 23 patients. However, results that are reported to be significant could not be replicated.

The study by Turhan *et al.* (2013) [31] was reported as a conference abstract and critically appraised by the company in Table B8z (abridged). This was probably a retrospective observational study and encompassed 105 patients in the Spectra cohort (159 procedures) and 127 patients in the Cobe Spectra cohort (188 procedures). It is probable some patients received both procedures and the mean age of Spectra Optia patients was older, introducing confounding. This paper was particularly poorly reported and the EAC recommends that caution be applied when interpreting results from it.

3.5.8 Studies comparing automated RBCx with simple manual 'top up' transfusions.

As discussed in Section 2.3.4, the EAC considers that top up transfusions are not a relevant clinical comparator to automated exchange transfusions, and should be judged to be out of scope. Most of these included studies were older than the other the other studies in the submission, with three studies predating 2000; these were Adams *et al.* (1996) [21], Hilliard *et al.* (1998) [23], and Singer *et al.* (1999) [52]. The other study, by Fasano *et al.* (2015) [5], has already been included as a key comparative study (Section 3.5.1.), although the inclusion of the top up transfusion arm was considered out of scope.

With the exception of Fasano *et al.*, these studies were non-comparative and of poor methodological and reporting quality, as evidenced in the company's own critical appraisal (company submission, Tables B8aa, ac, and ad). The

studies focussed on the use of automated apheresis reducing iron load compared to top up transfusions. The study by Adams *et al.* (1996) was essentially a sub-grouped case series that reported anecdotal evidence of improvements in iron overload or prevention of iron overload [21]. Hilliard *et al.* (1998) was a before and after study of patients switched from top up transfusion to RBCx with the Cobe Spectra system [23]. However, the study is subject to methodological limitations and statistical analysis was not undertaken. Finally, Singer *et al.* (1999) was a case series of eight patients who had been switched from top up transfusion to RBCx with the Cobe Spectra device [52]. Again, the methodological quality of this study was poor and robust statistical analysis was not undertaken.

3.5.9 Additional studies identified by the EAC

The EAC identified three additional papers through the additional literature search [16, 17, 56] and three additional papers through the supplementary sifting of conference abstracts [15, 18, 40] (see Section 3.3.).

The study by Asma *et al.* (2013) was published as a conference abstract [56]. Although some of the outcomes and results were not equivalent to the fully published study by Asma *et al.* in 2015 [19], the EAC considers it was highly likely that this study encompassed patients investigated in this study. Additionally, four of the patients discussed in the abstract were treated as emergencies, meaning this paper was technically out of scope. Therefore it was not considered further.

The study by Anwar *et al.* (2010) was a small retrospective case series (n = 4) published as a conference abstract that investigated the use of the depletion-exchange procedure of the Spectra Optia system [16]. The aims of the study were not clearly stated and although the authors stated the comparison was with the Cobe Spectra system without depletion, no comparator data was offered. It is unclear how patients were selected. The outcomes of this study focussed on resource use (particularly packed red blood cell use). However, it was unclear how results were calculated and no statistical analysis was described. These limitations, and the fact this was a very small study without a comparator, mean that although the study is technically in scope, the results should be viewed in context and with caution.

The study by Bahrani *et al.* (2015) was published as a conference abstract. This was a small case series (n = 6) of patients receiving the Spectra Optia system [17]. It was not clear how the patients were selected and there was no comparator data. The outcomes reported were largely narrative and there was no statistical analysis. Therefore, although this paper was technically in scope, it did not report usable numerical data.

The conference abstract by Anwar *et al.* (2015) [15] described 373 procedures that were undertaken with the Spectra Optia system (101 of which were depletion exchange). Selection of patients and their indications, and patient number, were not described, and although it is likely they were receiving chronic exchange, it is possible patients described in a previous study by this author were also included [16]. Although the authors described subgroup analysis in the methods, no usable results were presented and statistical analysis was not performed. The EAC thus concludes that although this paper was technically in scope, the reporting was too poor to provide useful data relevant to the decision problem.

The conference abstract by Kinney *et al.* (2015) reported a single centre's experience of switching from the Cobe Spectra system to the Spectra Optia system (standard and depletion exchange) over the course of a year [18]. However, this study was poorly reported. It was not possible to determine how patients were selected or what their indications were. The authors reported 29 RBCx performed with the Cobe Spectra system and 94 with the Spectra Optia system, but did not state how many patients were investigated. Although three cohorts (derived from quarterly intervals) were described, it appeared that treatments used in these were mixed between systems and procedures. As it was not possible to disaggregate this data, the EAC concluded it was not usable.

A recent conference abstract by Trompeter *et al.* (2015) [40] contained data already reported elsewhere and has already been summarised. Therefore this paper was not considered further.

3.5.10 Summary of quality of other studies

Overall, the quality of the non-comparative studies submitted by the company, and those studies additionally identified by the EAC, was poor. These were predominantly retrospective studies prone to significant confounding and bias, particularly in terms of patient selection and reporting of results. The overall reporting of the studies was poor and consequently interpretation of the results in a context that was generalisable to NHS practice was not always possible. The EAC has summarised the quality of the papers that were published in peer-reviewed journals in Table 3.6. Results from these studies individual studies are considered on their own merits when they are relevant to the decision problem (Section 3.10).

Table 3.6. *Quality assessment of single armed studies of Spectra Optia and Cobe Spectra*.

Study author	Method quality	Reporting quality	Potential for confounding and bias	Overall uncertainty
Quirolo *et al*. (2015) [11] Spectra Optia	Good. Prospective study with pre-defined aims.	Medium. Full peer-reviewed article but some important details not reported.	Medium. Patient selection and other confounders.	Medium. Provides useful information on the Spectra Optia system including depletion exchange.
Bavle *et al*. (2014)[8]	Medium Retrospective comparative study with an attempt at matching controls	Medium Full peer-reviewed article but some important details not reported.	High Patient selection, historical controls and other confounders	Medium Adequately designed study but primary outcome of growth in children was of peripheral interest to the decision problem.
Billard *et al*. (2013) [43]	Medium Case series with consecutive recruitment. Limited before and after analysis.	Good	High No controls.	High Consecutively and reported with enough granularity to allow for analysis by third party.

Study author	Method quality	Reporting quality	Potential for confounding and bias	Overall uncertainty
Kalff *et al*. (2010) [9]	Poor Single-centre retrospective case series, with incomplete medical records	Medium Full peer-reviewed article but some important details not reported.	Medium. Patient selection and other confounders.	Medium Validity was limited by the lack of a comparator arm, and before/after comparisons could not be performed
Masera *et al*. (2007) [10]	Medium Single-centre, retrospective review of a cohort over 11 years.	Poor Full peer-reviewed article but important details not reported.	High Patient selection and several confounding variables not controlled for.	High Concerns with generalisability of the results to current practice.
Sarode *et al*. (2011) [12]	Medium Retrospective comparative review with historical controls	Medium Full peer-reviewed article but some important details not reported.	High Patient selection, historical controls and other confounders	Medium Study describes a comparison between two modes for Cobe which is not directly in scope
Shrestha *et al*. (2015) [13]	Medium Retrospective observational	Poor Full peer-reviewed article but	High Patient selection, data	High Study compares two types of

Study author	Method quality	Reporting quality	Potential for confounding and bias	Overall uncertainty
	cohort study	important details not reported.	collection and other confounders	venous access which is not directly in scope.

3.6 Results

Results from the individual included studies were summarised by the company in Tables B9a to B9ad of the company submission. The EAC has not repeated this work in order to avoid unnecessary duplication and document redundancy. The company also summarised the results according to the scope outcomes in Tables B12a to B12f (pages 125 to 130). Again, and for the same reasons the EAC has not replicated this work. Instead the EAC has:

- Cross referenced all the reported results in the company's tables with the original published papers (Section 3.6.1).
- Summarised the results from the comparative studies and other peer reviewed studies (Section 3.6.2) and additional studies (Section 3.6.3), adding context to possible limitations caused by the poor methodological quality of the primary research.
- Examined the company's interpretation of outcomes of the clinical evidence and the company's claimed benefits (Section 3.8).
- Summarised the opinion of EAC clinical experts on certain key points of system efficacy, patient pathways, and future research (Section 3.6.6).

It should be noted that there are difficulties in interpreting results from the included studies relative to each other. For example this may be because of: differences in research methodology; difference in units reported (such as absolute or relative to body weight); reporting of absolute results or differences relative to baseline (with baseline results typically not being reported); and differences in resource or monetary values (which vary by country and date).

3.6.1 Cross reference of results

The EAC has cross-referenced all the company's tabulated results with each other and the original published data, The EAC found the results to be very accurate to the source material with only a small number of (probable) transcriptional errors that did not alter the meaning of the submission in any significant way.

3.6.2 Summary of results comparative and peer-reviewed studies

A summary of the results from the key studies (six comparative and one single-armed prospective are listed in Table 3.7.

Table 3.7. *Summary of the results from the comparative studies.*

Study	'Primary' results*	'Secondary' results	Fit with scope	Other comment
Cabibbo *et al.* (2005) [2] Retrospective observational study	**Clinical improvement**: 20/20 patients. **Procedure time**: Cobe Spectra: 70 mins Baxter CS3000 Plus: 240 minutes MCS+ Haemonetics: 180 mins	Ferritin level Antiglobulin tests (direct/indirect). Single and standard red donor cells used. Blood pathology.	Procedure time, but no comparison with manual exchange reported. Distributional data of procedure time not reported (therefore statistical differences can't be calculated).	'Clinical improvement' not defined. All secondary results reported per patient, no statistical analysis comparing automated and manual RBCx reported. Unclear when outcomes were measured.
Dedeken *et al.* (2014) [3] Before and after study	*Spectra Optia (1st year, 2nd year) vs Manual* RBCx (median, range). **HbS%:** 40% (28.5 – 42%) 46% (31 – 48%)	*Spectra Optia (1st year, 2nd year) vs Manual* RBCx (median, range). **Duration of procedure**: 87.3 min (75.5 – 126min) 91 min (64 – 154min) 245 min (195 – 360min), p=0.0002	HbS%, duration of procedure, interval between procedures, RBC requirement all outcomes in cope. Ferritin levels are a proxy for iron overload and requirement for chelation (specified in scope).	Unclear what p values relate to, is it manual RBCx with first or second year of automated RBCx, or something else? Costs per year of treatment were also stated but method of calculation was not. Results should be treated with

Study	'Primary' results*	'Secondary' results	Fit with scope	Other comment
	33.5% (25 - 42%), p=0.02 **Ferritin** (µg/L): 255 µg/l (52-811) 148 µg/l (9-622) 666 µg/l (182-1512), p<0.001	**Interval between procedures**: 34 days (28 - 35.5) 42 days (28 - 42) 28 days (21 - 29), p<0.0001 **RBC requirement (ml/Kg)**: 32.2 (27.4-36.1) 30.0 (26.8-36) 18.3 (15.1-20), P<0.0001 **RBC requirement (units)**: 67.0 (49-120) 65.5 (38-137) 39.5 (15-79), p<0.0001		caution (see section 3.4.1).
Duclos *et al.* (2013) [4]	*Cobe Spectra vs manual RBCx* **Pre-exchange HbS%**: 47.5 (22	*Cobe Spectra vs manual RBCx* **Blood volume transfused (ml/Kg)**:	HbS%, patient haematocrit, and blood volume transfused all in scope.	Figures in parentheses are assumed to be range. Post-exchange HbS% values not

Study	'Primary' results*	'Secondary' results	Fit with scope	Other comment
Retrospective case-matched series	to 84) 45.6 (20.6 to 81), p=0.05 **Pre-exchange Hb (g/L)**: 94 (84 to 105) 91 (73 to 121), p=n/s **Pre-exchange Hct (%)**: 25.5 (19 to 31.6) 27 (22 to 35), p<0.001) **Pre-exchange platelet count (giga/L)**: 467 (148 to 698) 594 (123 to 807), p<0.001	41 (19.6 to 60) 11.1 (6.6 to 20), p<0.0001 Subgroup analysis in exchanges performed <40 days since previous exchange.		available. Subgroup analysis deemed not helpful by EAC.
Fasano *et al.* (2015) [5] Retrospective	*Automated RBCx vs partial manual RBCx* **Average HbS (%)**:	*Automated RBCx vs partial manual RBCx* **Liver iron content** (where at least	HbS%, iron overloading measurements (ferritin and liver iron content) and alloimmunisation in the	Unclear if "average" HbS (%) and changes in ferritin are pre- or post-procedure. Comparators were partial or top

Study	'Primary' results*	'Secondary' results	Fit with scope	Other comment
observational study.	36% vs 34% **Average ferritin change (ng/mL/month)**: -61 (-161 to 17) vs 19 (-42 to 106), p<0.001	2 records available (mg/g/year): 1.6 (-9.2 to 10.9) vs -5.7 (-12.0 to 0.2), p=0.0235 **Alloimmunisation**: 0.51/100 units (including simple transfusion) vs 0.5/100 units	scope.	up exchange which are possibly not in scope, as neither are 'iron neutral'.
Kuo *et al.* (2015) [6] Retrospective observational study (comparison of centres)	*Spectra Optia RBCx vs manual RBCx* **Mean pre-procedure HbS** (%) (median, range). 50 (27 to 76) vs 55 (16 to 72), p=0.162 **Less than 2/3rd proportion of RBCx sessions within target:** 19/30 vs 19/21, p=0.048 OR 4.72 (95% CI 0.89 to 25.20) [not significant] **Median post RBCx**	*Spectra Optia RBCx vs manual RBCx* **Packed RBC utilisation (ml)**: 241 vs 127, p<0.0001 **Packed RBC utilisation (units)**: 55 vs 31, p<0.0001 **Duration of procedure (min)**: 115 vs 257, p<0.0001 **Frequency of sessions (weeks)**. Mean (SD):	HbS (%), haematocrit, RBC use, duration of procedure, frequency of procedure, and adverse events are within scope.	Reporting confusing for some outcomes, for example HbS(%) appears to be a median measurement of patient mean levels. There was a lack of consistency of presentation (means, median, ranges, SD, OR are all presented). The measurement of proportion of sessions reaching target appears arbitrary. Paper is more focussed on targets than the system used to

Study	'Primary' results*	'Secondary' results	Fit with scope	Other comment
	haematocrit: 0.31 (0.23 to 0.35) vs 0.31 (0.25 to 0.38), p=0.931 **Ferritin trend (µg/L/day)****: -0.29(±2.027) vs -0.068(±1.43), p=0.439	6.66 (1.65) vs 4.86 (1.8), p=0.0001 **Adverse events**: 11/30 vs 10/21, p=0.7953 **Peripheral venous access**: 1/30 vs 14/21, p<0.0001 **Procedures requiring additional top transfusions****: 0/30 vs 11/30		achieve this.
Woods *et al.* (2014) [7] Retrospective cohort study	*Spectra Optia vs manual RBCx* **Achievement of HbS target**: 0.80 (0.40 to 1.0) 0.50 (0.28 to 0.90), p=0.27 **Ferritin concentrations (ng/ml)**: 875 (578 to 2659)	*Spectra Optia vs manual RBCx* **Catheter complications**: 15/21 1/17, p<0.001	HbS, ferritin concentrations, and catheter complications specified in scope.	Difficult to interpret results due to patients receiving mixed treatments, unclear timing of outcomes, and patients switching treatments (including 5 patients from Spectra Optia to manual RBCx because of catheter complications.

Study	'Primary' results*	'Secondary' results	Fit with scope	Other comment
	1527 (731 to 2568), p=0.56			

* Primary and secondary outcomes not usually specified. The relative 'importance' of results interpreted from author's aims and/or reported in abstract or discussion. Resource use generally considered as secondary aims.

** Additional data from Kuo *et al*. conference abstract [57].

Table 3.8 *Summary of the results from the peer-reviewed studies*

Study	'Primary' results*	'Secondary' results	Fit with scope	Other comment
Quirolo *et al.* (2015) [11] Prospective observational study (with subgroup analysis) Spectra Optia	**Ratio of FCRa** (acceptable range 0.75 to 1.25): Evaluable population: 0.90±0.17 RBCx: 0.90 ± 0.17 Depl/RBCx: 0.89 ± 0.15 Children: 0.90 ± 0.18 Adults: 0.89 ± 0.14 p≥0.05 **Pre-procedure HbS(%)**: Evaluable population: 37.97±12.81 RBCx: 37.00 ± 13.96% Depl/RBCx: 35.13 ± 8.68% Children: 39.83 ± 14.03% Adults: 34.24 ± 9.14% p≥0.05 **Post-procedure HbS(%)**: Eavluable population: 13.88±6.03 RBCx: 14.11 ± 6.22 Depl/RBCx: 13.23 ± 5.64	**Run time (mins)**: Evaluable population: 90 ± 22 RBCx: 92 ± 24 Depl/RBCx: 86 ± 16 Children: 81 ± 16 Adults: 95 ± 24 Children vs adult: p<0.05 **RBC replacement volume (mL)**: Evaluable population: 1895 ± 670 RBCx: 2016 ± 729 ml Depl/RBCx: 1562 ± 281 Children: 1449 ± 260 Adults: 2118 ± 702 Depl/RCBX vs RCBX p<0.05 Children vs adults p<0.05	Primary outcome (ratio of FCRa) not in scope. HbS(%), Hct target, run time, and RBC replacement in scope.	Inadequate description of baseline characteristics. Mean averages with SD stated. Single armed study incorporating sub group analysis of depletion vs standard RBCx and children vs adults. Treatment modalities are mixed causing confounding which is not controlled for. No significant differences between subgroups not directly related to weight and age.

Study	'Primary' results*	'Secondary' results	Fit with scope	Other comment
	Children: 14.7 ± 6.44 Adults:12.24 ± 4.87 p≥0.05 **Final measured Hct (%)**: Evaluable population: 31.4 ± 2.7 RBCx: 30.8 ± 2.6 Depl/RBCx: 32.9 ± 2.2 Children: 31.4 ± 3.0 Adults: 31.3 ± 2.5 p≥0.05	**RBC replacement volume (mL/kg)**: Evaluable population: 15.4 ± 5.1 RBCx: 14.7 ± 5.0 Depl/RBCx: 17.2 ± 4.9 Children: 18.6 ± 3.5 Adults:13.8 ± 5.0 p≥0.05		
Bavle *et al*. (2014) [8] Retrospective observational comparative study Cobe Spectra	N/A[a]	N/A[a]	The primary outcome of interest, growth in children, was in scope but of peripheral interest only to the decision problem	Study confounded by the use of historical controls. 2 matched controls were found for 28 study subjects, but only 1 matched control was found for 8 of the subjects. No statistically different growth parameters for the study subjects and matched controls.
Billard *et al*. [43]	Serum ferritin levels "no	RBC usage whole population: 332mL/Kg (range 280 to 370	Iron overload and requirement for chelation	EAC calculated mean ferritin levels as 407.6 ng/mL (SD 376.4)

Study	'Primary' results*	'Secondary' results	Fit with scope	Other comment
	significant changes" (p=0.267)	mL/Kg) RBC usage per procedure 55 mL/Kg (range 47 to 63 mL/Kg)	therapy (extrapolation from ferritin levels) Donor blood usage	before study and 428.9 ng/ml (SD 561.2) after study. 17/18 patients were not on chelation.
Kalff *et al*. (2010) [9] Retrospective case series Cobe Spectra	**Procedural data** Median number of RBCX procedures per patient: 68 (7-90) **Red cell usage** Total red blood cell units exchanged: 299 (43-493) Red cells per exchange: 5.7 (4.4-6.1) **HbS levels** Pre-procedure HbS (%): 47.4 (40.7-59.3) Post-procedure HbS (%): 25.5 (18.5-32.6)	**Ferritin levels** Low baseline level (µg/l) Pre-RBCX: <300 Post-RBCX: <600 Moderate baseline level (µg/l) Pre-RBCX: 465 (311-582) Post-RBCX: 282 (69-361) High baseline level (µg/l) Pre-RBCX: 2700-10700 Post-RBCX: 900-7700 **Acute sickle cell-related events** 16 acute events in 5 patients in 846 months of cumulative patient follow up Painful crises: 13/16	Primary and secondary outcomes within scope.	HbS levels reported as mean with SD. Medium ferritin levels reported as median and range. The lack of a comparator arm and the usual shortcomings associated with observational studies of this nature (in terms of confounders and bias) make interpretation of the results difficult. Some medical records were incomplete or destroyed and patients had been transferred from another institution. Baseline data prior to commencement of RBCx may not be reliable and should be treated with caution.

Study	'Primary' results*	'Secondary' results	Fit with scope	Other comment
		Acute chest syndromes: 3/16		
Masera *et al*. (2007) [10] Retrospective review of routine data Cobe Spectra	**HbS levels** Pre-procedure HbS (%): 63 (49-83) Post-procedure HbS (%): 20 (7-34) **Ferritin change (ng/l)** Pre-RBCX: 1175 (45-2648) Post-RBCX: 915 (270-1866)	**Red cell usage** RBCs used for each procedure was approximately 30 ml/kg body weight **Hospital admissions/year** Pre-RBCX: 1.7 (0.2-4) Post-RBCX: 0.69 (0-1.8) RBCX + hydroxyurea: 0.24 (0-1) **Pain crises/year** Pre-RBCX: 4.8 (0.2-12) Post-RBCX: not reported RBCX + hydroxyurea: 1.79 (0-5.5)	Primary and secondary outcomes within scope.	All outcomes reported as mean with range. Patient selection was not clear and confounding variables were not controlled for. Poorly reported and confusing study. The EAC recommends that data taken from this study is used with caution.
Sarode *et al*. (2011) [12]	**Haematocrit** Pre- IHD-RBCX: 27.8% ± 2.4 Post- IHD-RBCX: Hct achieved: 32.8% ± 1.6 **HbS levels**	**Packed red blood cell utilisation (mL/kg)** IHD-RBCX: 35.5 ± 4.1 C-RBCX: 39.5 ± 4.6 **Procedural data**	Primary and secondary outcomes within scope, however, the study describes a comparison between two modes for the Cobe Spectra system which is not directly relevant to	Values reported as mean with standard deviation. Issues of confounding and bias. Unclear selection or matching of the 6 historical controls.

Study	'Primary' results*	'Secondary' results	Fit with scope	Other comment
	Pre- IHD-RBCX: HbS (%): 41.8 ± 6.1 Post- IHD-RBCX: HbS (%): 9.8 ± 2.4	Procedure duration (minutes) IHD-RBCX: 103.9 ± 12.4 C-RBCX: 107.3 ± 6.7 Procedure interval (days) IHD-RBCX: 52.9 ± 6.5 C-RBCX: 37 ± 7.0 Procedures per year per patient IHD-RBCX: 9.8 C-RBCX: 7.0 **Adverse events (overall)** IHD-RBCX: 18.5% (109/594) C-RBCX: 13.5% (14/112)	the scope.	
Shrestha *et al*. (2015) [13] Retrospective observational cohort study[b] Cobe Spectra	Duration of procedure (hours): 2 ± 1.6	Red blood cell utilisation (units): 6.3 ± 1.7 Hct target achieved: 87% HbS target achieved: 95%	The study is of limited immediate relevance to the decision problem.	Values reported as mean with standard deviation. Issues of confounding and bias, particular risk of selection bias.

Study	'Primary' results*	'Secondary' results	Fit with scope	Other comment
[a] No quantifiable outcomes can be reported from this study [b] Only relevant data from the whole cohort have been reported.				

3.6.3 Summary of results from additional studies identified by EAC.

For completeness, a summary of the results from the additional studies identified by the EAC (which were considered not to be duplicate studies or out of scope) is reported in Table 3.9.

Table 3.9. *Summary of results of additional studies identified by EAC*.

Study	'Primary' results*	'Secondary' results	Fit with scope	Other comment
Bahrani *et al.* (2011) [17] Retrospective case series	Data on 6 patients presented: **Pre-procedure Hct (%)**: Mean: 26.3 (range 24 to 32) **Post-procedure Hct (%)**: Mean 27.7 (range 25 to 31) **Pre-procedure HbS(%)**: Mean: 74.1 (range 65 to 80) **Post-procedure HbS(%)**: Mean: 29 (range 14 to 45)	Data on 6 patients presented: **RBCs replaced (ml)**: Mean 1193 (range 680 to 1831)	Hct, HbS and RBC replaced are in scope.	Results presented per individual patient and descriptive statistics provided by EAC.
Anwar *et al.* (2010) [16] Retrospective case series	Data on 4 patients presented: **Initial Hct (%)**: Mean 21.0 (range 30 to 40)	**RBC saved (ml)**: Mean 194.8 (range 87 to 376)	Hct and RBC replaced are in scope.	Results presented per individual patient and descriptive statistics provided by EAC.

Study	'Primary' results*	'Secondary' results	Fit with scope	Other comment
	Hct after depletion (%): Mean 24.3 (range 24 to 25) **Hct post-procedure**: Mean 27.8 (range 27 to 30)			
Anwar *et al.* (2015) [15] Retrospective observational study	**Pre-procedure Hct (%)**: Range 26 to 37.9	**Red cells saved (ml)**: Range 45 to 521		Results as reported not usable.
Kinney *et al.* (2014) [18]	Four quarterly outcomes reported: **Quarter 1** (mean): Pre-procedure Hct (%): 27.2 Pre-procedure HbS(%): 48.5 Proportion post-procedure Hct target met (%): 83	None	Hct (%), HbS (%), targets, and blood units used are within the scope.	Study aimed to observe transfer of RBCx with Cobe Spectra to Spectra Optia. However, mixed treatments were used during quarters so a comparison in untenable. No statistical analysis reported.

Study	'Primary' results*	'Secondary' results	Fit with scope	Other comment
	Proportion post-procedure FCR met (%): 100 Average units used: 8.2 **Quarter 2** (mean): Pre-procedure Hct (%): 25.7 Pre-procedure HbS(%): 39.7 Proportion post-procedure Hct target met (%): 98 Proportion post-procedure FCR met (%): 98 Average units used: 8.0 **Quarter 3** (mean): Pre-procedure Hct (%): 25.3 Pre-procedure HbS(%): 47.3 Proportion post-procedure Hct target met (%): 100 Proportion post-procedure FCR met (%): 100			

Study	'Primary' results*	'Secondary' results	Fit with scope	Other comment
	Average units used: 8.4			

* Primary and secondary outcomes not usually specified. The relative 'importance' of results interpreted from author's aims and/or reported in abstract or discussion. Resource use generally considered as secondary aims.

3.6.4 Critique of company's interpretation of the clinical evidence

The company summarised the results of all the studies according to outcome in company submission Tables B12a to B12f, which the EAC has cross-referenced and found to be an accurate record of the results. The company interpreted each of these outcomes with a short narrative in company submission section 7.9.1, from which overall conclusions in the clinical evidence were made. The EAC has critiqued each of these interpretations in the order the outcome was presented in the scope [1]. This takes into account not only the results as published, but also the quality of the studies the results were reported in, and the level of uncertainty or confidence this implies.

Abnormal haemoglobin (HbS%)

In the scope, this was fully described as "Percentage of total haemoglobin that is HbS (HbS%), relative to target percentage (usually <30%)". The EAC considered that all measures of HbS (%) were potentially relevant to this outcome. Abnormal haemoglobin levels are considered important as they may be a surrogate outcome for the prevention of complications of SCD, with achievement of HbS targets (dependent on indication, but typically 30%) being associated with reduced mortality and morbidity [58, 59].

The two comparative studies that the EAC considered were of higher methodological quality both reported values for pre-procedural HbS, which as the company discussed, can be regarded as a proxy measurement for chronic HbS levels. In the case matched study by Duclos *et al.* (2013) [4], pre-procedural HbS% was found to be significantly higher for manual RBCx than for automated RCBX. However, this difference was marginal and of uncertain clinical significance, and could have been influenced by the 'centre effect'. In the study by Kuo *et al.* (2015) [6], there were no significant difference in pre-procedural HbS levels. Post-procedural HbS levels were not explicitly reported in this study, but the author's reported that there was a significant improvement ($p = 0.048$) in the proportion of patients who had reached two thirds of their HbS targets. However, this threshold appears to have been set arbitrarily, and the significance was lost when the odds of target success were calculated (OR 4.72 [95% CI 0.89 to 25.20]). Therefore these studies do not provide convincing evidence that automated RBCx is associated with better control of HbS than manual exchange.

In the comparative 'before and after' study by Dedeken *et al.* (2014) [3], median HbS levels were significantly lower with manual RBCx (this is contrary to what was reported in the company's narrative). However, this result might have been confounded by disease progression (all subjects received Spectra Optia subsequent to manual RBCx). The comparative study by Fasano *et al.*

(2015) [5] showed no significant difference in ‘average HbS’ but this was also confounded by the use of an inappropriate comparator (top up transfusions and partial exchange RBCx). The prospective study by Quirolo *et al.* (2015) [11] showed no significant effect of depletion RBCx over standard RBCx on HbS levels using the Spectra Optia system. The EAC does not consider that the other single armed studies are of value in addressing this outcome in the context of the decision problem.

In conclusion, the current evidence base on the effects of automated RBCx on HbS compared with manual RBCx is equivocal. This does not preclude the fact that the Spectra Optia system might be beneficial for this outcome, but currently there appears to be no direct evidence that the control of HbS is different between automated and manual RBCx.

Duration of exchange procedure

Several of the comparative studies measured duration of exchange procedure as an outcome, which has implications for resource use and patient experience. The UK-based comparative study of Kuo *et al.* (2015) [6] reported a mean duration of 115 minutes for the Spectra Optia device (1 hour 55 minutes) compared with 257 minutes for manual RBCx (4 hours 17 minutes, $p < 0.0001$). The comparative study by Dedeken *et al.* (2014) also reported a significant reduction in procedure duration in favour of the Spectra Optia system (91 minutes [1 hour 31 minutes] compared with 245 minutes [4 hours 5 minutes], $p = 0.002$) [3]. These results are consistent with the prospective study by Quirolo *et al.* (2015) [11], which reported an average run time of 90 minutes for the Spectra Optia system. The study by Cabibbo *et al*. (2005) reported an average run time of just 70 minutes, but no individual or distributional data (or data on manual RBCx) were reported [2].

Based on these studies, the EAC considers there is unequivocal evidence that the use automated RBCx with the Spectra Optia system (in either standard or depletion modes) reduces procedure time, and that this reduction is likely to be operationally significant. The company’s claim that “Automated red blood cell exchange with this device is faster than manual red blood cell exchange with treatment lasting approximately 2–3 hours in comparison to 4–8 hours. This makes the procedure more convenient for patients which may improve compliance” [1] is largely true, although the procedure time of manual RBCx is likely to be variable depending on individual practice, disease severity and targets. The amended claim in the submission (claimed benefits, page 136) of 4 to 6 hours for manual and 1.5 to 2.5 hours for automated RBCx seems a reasonable estimate.

Frequency of treatment

The frequency of treatment (time period between exchange procedures during the treatment of chronic SCD) is not a straight forward outcome. The EAC understands from clinical experts (see EAC Correspondence Log) that the frequency of treatment is decided on several factors, including, but not limited to, indication, target HbS (typically 30% or 50%), symptoms, and the patient's individual RBC proliferation and sickle rate. Usually the frequency of RBCx will be determined depending on pre-procedural RBCx HbS levels and symptoms (typically initial frequency is 6 to 8 weeks) and this will then be modified according to blood results and clinical status. This process was not discussed in any of the included studies which were generally reliant on routine retrospective data which, however, would indirectly reflect this process.

Two of the comparative studies investigated frequency of RBCx as an outcome. The UK-based study by Kuo *et al.* (2015) [6] reported an interval between treatments of 4.86 weeks for manual RBCx compared with 6.66 weeks for Spectra Optia (this would be a difference of approximately 12.5 days, p = 0.0001). The study by Dedeken *et al*. (2014) reported an average interval between procedures of 28 days compared with 34 and 42 days for the first and second years use of the Spectra Optia system respectively (p = 0.0002). Procedure frequency for automated RBCx was similar for the single armed studies of the Cobe Spectra device [9, 43]; however the EAC did not accept that the single-armed studies on manual RBCx were useful to the decision problem, so no further data were available for this treatment method.

Based on limited clinical evidence, the EAC considers that the use of automated RBCx with the Spectra Optia device does reduce the frequency of treatments required, and this is likely to be operationally significant. From the available comparative data, it is likely that the use of Spectra Optia may (after a period of adjustment) result in treatment cycles of between 12 to 20 days longer than manual exchange, although there is considerable uncertainty regarding the size of this effect. The company's claimed benefit that "Automated red blood cell exchange using the Spectra Optia Apheresis System has a longer clinical effect than manual red blood cell exchange meaning that patients would require treatment only every 6–8 weeks in comparison with every 3–4 weeks" [1] is probably an overestimate of this effect. The revised company's estimate in the submission (claimed benefits, page 136) of "4-5 weeks for manual and 6-7 weeks for automated [RBCx]" is probably nearer the true figure, but is still prone to residual uncertainty due to the limited number of reporting studies and the poor study methodology used by these studies.

Patient haematocrit

The full outcome in the scope is “Patient haematocrit (measure relative to prescribed target for therapy)” [1]. Two of the comparative studies reported on this outcome, which were the ‘between centres’ studies the EAC considered to be of better quality than the others. In the study by Duclos *et al.* (2013) [4], pre-exchange haematocrit was found to be significantly lower in children receiving Spectra Optia compared with those receiving manual RBCx (25.5% compared with 27%, $p < 0.001$). In the study by Kuo *et al.* (2015), there was no difference found between the median post transfusion haematocrit between the transfusion types, which were both 0.31 ($p = 0.931$). Additionally the prospective study by Quirolo *et al*. (2015) reported that the post-procedure haematocrit was 31.4% (±2.7% SD) [11]. There was no significant differences seen between adults and children or people receiving standard or depletion exchanges.

In conclusion, the EAC considers that there is some evidence pre-procedural haematocrit may be slightly lower with the Spectra Optia system, although this could be an artefact of study methodology and the clinical importance of this is uncertain. It is likely that the Spectra Optia is equivalent to manual RBCx in maintaining post-procedural haematocrit around the 30% level. In the scope, the company claimed “The Spectra Optia Apheresis System maintains haematocrit levels which prevents iron overloading” [1]. In the EAC’s opinion, there is no evidence the Spectra Optia system is superior to manual RBCx in this respect.

Iron overload and requirement for chelation therapy

Changes to the risk of iron overload is usually measured by the intermediate outcome of ferritin (measured as absolute value or as a rate) and/or as liver iron concentration. Four of the comparative studies identified reported serum ferritin as an outcome, but this did not include the full versions of the two studies of better methodological quality.

In the study by Cabibbo *et al.* (2005), the trend of ferritin level was reported in each subject [2]. For patients receiving manual RBCx the trend was upwards for all patients (7/7). For patients receiving automated RBCx (several systems), the trend was downwards in 7/13, stable in 5/13, and increasing in 1/13. However, the EAC cautions that data from this study is likely to be highly compromised.

In the study by Dedeken *et al.* (2014) there was a trend for decreased ferritin levels with use of the Spectra Optia system [3]. From a baseline of 666 µg/l (range 182-1512 µg/l), average ferritin levels decreased to 148 µg/l (9-622 µg/l) in year 1 and 255 µg/l (52-811 µg/l) in year 2 of using Spectra Optia (this was reported as significant although it is unclear how the test was performed).

Two patients who were receiving chelation treatment were able to stop after 1 and 10 procedures of Spectra Optia respectively. However, a major limitation of this study was that there was no parallel control group, so it is not possible to speculate how ferritin levels would have changed had they been kept on manual RBCx.

In the abstract version of the study by Kuo *et al*. (2012), a greater trend toward ferritin reduction was reported in the spectra Optia group at -0.29 µg/L/day (±2.027 SD) compared with -0.068 µg/L/day (±1.43 SD). However, this was not significant (p = 0.439) [57] and was not reported in the full publication of the study [6].

In the study by Fasano *et al*. (2015) it was reported that ferritin levels dropped by an average of -61 ng/ml/month in patients receiving Spectra Optia, whereas they increased by an average of 19 ng/ml/month in those receiving the control (p < 0.001). This study also found a significant increase in liver iron content over the study period (-5.7 mg/g/year for Spectra Optia compared with +1.6 mg/g/year for controls). However, the controls consisted of top up exchange and partial manual exchange, neither of which are considered as iron neutral therapies or are in scope.

In the study by Woods *et al.*, no significant difference in ferritin concentration were found between Spectra Optia and manual RBCx [7], with those receiving Spectra Optia having an average concentration 875 ng/ml (range 578 to 2659 mg/ml) compared with 1527 ng/ml (range 731 to 2568 ng/ml) for manual RBCx (p=0.56).

Although ferritin and liver iron content were outcomes reported in several single-armed studies of the Spectra Optia system [48-50] and the Cobe Spectra system [9, 10, 20], it is difficult to interpret these studies without a control arm and results were conflicting. In addition, there were confounding factors such as the use of concomitant chelation in several of these studies.

In conclusion, the EAC considers that the evidence for the Spectra Optia system in reducing levels of ferritin, compared with manual RBCx, is equivocal. Both modalities are regarded as iron neutral, and although automated exchange may provide advantages concerning this, this has not yet been adequately demonstrated by the evidence presented. However, it is likely that the Spectra Optia system is at least non-inferior for this outcome. In the scope, the company claimed “Treatment with the Spectra Optia Apheresis System could allow patients to reduce or cease iron chelation treatment due to reduced iron overloading” [1]. The EAC does not consider that this claim has been substantiated on the balance of evidence presented.

Clinical outcomes

In the scope, this is fully described as “Clinical outcomes including frequency of stroke, multi-organ failure, acute chest syndrome and pain crises” [1]. These outcomes have not been quantitatively described by any of the studies included in the clinical evidence section of the submission. This is largely because the identified studies were mainly retrospective observational studies that reported routine data with a focus on the procedures themselves, rather than the clinical outcomes associated with the procedures. Additionally the period of study and study size was often limited, and as all the studies were observational, the lack of a controlled comparator meant that the occurrence of clinical events could not be solely attributed to the RBCx systems.

It may be possible to relate a surrogate parameter, such as HbS (%), with the likelihood of complications of SCD occurring, and this has been demonstrated in previous studies where reduced HbS levels have been associated with improved prevention of stroke in children [58-60]. However, the evidence for Spectra Optia being associated with an incremental improvement in surrogate parameters compared with manual RBCx is equivocal. Therefore, the EAC considers that the company’s claims that use of the system could lead to “improved outcomes include: reduced incidence of stroke, reduced frequency and severity of pain crises, reduced incidence of acute chest syndrome” have not been substantiated. This also applies to the claim of “Reduced complications from sickle cell disease leading to reduced hospitalisations and associated treatment” [1].

Quality of life

Quality of life was not addressed directly or indirectly by any of the included studies. Therefore the claim that the Spectra Optia system may lead to “improved general quality of life” [1] (compared with manual RBCx) has not been tested so is unsubstantiated.

Length of hospital stay

The length of hospital stay was not an outcome investigated by any of the included studies. However, it is reasonable to assume that because procedure time is significantly shorter with the Spectra Optia device, then so will length of outpatient stay be shorter. Barring complications, it is highly unlikely that an overnight stay will required, which is sometimes the case with manual RBCx. This would substantiate the claim by the company that reduced hospital stay is required when using the Spectra Optia system [1].

Staff time and staff group/grade

This outcome was not addressed by any of the included studies in the company submission. Clinical experts have advised the EAC that both manual RBCx and the Spectra Optia system require staff with specialised training. However, manual RBCx is considered to be more labour intensive, especially if vascular access is poor (see EAC Correspondence Log). This outcome concerns resource use only and is considered further in the economic submission section (Section 4.2.6).

Frequency of top-up transfusion required to treat sickle cell complications

No studies were identified which reported this outcome.

Ease of venous access, bruising and haematoma

There is considerable variation in achieving venous access when using automated RBCx, and in practice this may be particularly problematic in paediatric populations. Many patients with SCD have poor venous access and may require the placement of a femoral line or placement of indwelling dual-lumen ports, with or without radiographic assistance.

Many of the studies reported that venous access was a limiting factor in treating patients with automated RBCx. For example, in the study by Cabibbo *et al.* (2005), some of the patients who received manual RBCx did so because there was inadequate access to allow treatment with automated RBCx [2]. Similarly, difficulty in venous access was described as a complication in 14/60 patients in the study by Dedeken *et al*. (2014) [3]. In the study by Kuo *et al*., peripheral venous access was only achieved in 1/30 patients receiving Spectra Optia compared with 14/21 receiving manual RBCx [6].

Device related adverse events

The company failed to provide a statement in section 7.9.1 of their submission of principal findings from the clinical evidence regarding any risks relating to adverse events from the technology.

As noted by the company, no identified studies were powered to analyse adverse events. A statistically significant difference in catheter complications in children and teens receiving regular RBCx for stroke prevention was reported by Woods *et al*. (2014) [7], comparing the Spectra Optia to manual RBCx (15/21, 71.4%, versus 1/17, 5.9% of patients; $p<0.001$). Within the study population, 5 patients were switched from Spectra Optia to manual RBCx because of catheter complications. The authors attributed the increase in catheter complications to the use of large-bore double-lumen implantable port access. Patel *et al* (2013)[45] reported 4/32 (12.5%) patients having had

major bleeding from the femoral line site, leading to a Hb drop requiring transfusion or readmission. Of the original 40 study subjects, 5 had discontinued the automated RBCx programme due to problems with tolerating the procedure or other complications.

Hospital admissions

None of the comparative studies included hospital admission as an outcome. The single armed study by Sturgeon *et al*. (2009) reported a significant reduction in hospital admission in a cohort of patients receiving regular (8 weekly) treatments with Spectra Optia, from 34.8 days/year before automated RBCx to 7.60 days/year ($p < 0.005$). This outcome is confounded by indication. Other studies have also reported hospital admissions reduced after initiation of automated RBCx regimens [9, 10]. However it is not possible to draw firm conclusions from non-comparative observational studies. For this reason, the EAC considers the company's claim that "Reduced complications from sickle cell disease leading to reduced hospitalisations and associated treatment" [1] has not been proven.

Donor blood usage

It is an accepted fact that donor blood usage is higher with automated RBCx than with manual RBCx, and several comparative studies have attempted to quantify this. The before and after study by Dedeken *et al.* (2014) [3] reported that manual RBCx used 18.3 ml/Kg of packed RBC, compared with 32.2 ml/Kg and 30.0 ml/Kg in the first and second years use of Spectra Optia respectively ($p < 0.0001$). In terms of total units used, this was 39.5 compared with 67.0 (first year) and 65.5 (second year, $p < 0.0001$). The difference in RBC use reported in the study by Duclos *et al.* was greater, with 11.1 ml/Kg being used for manual RBCx compared with 41 ml/Kg for the Cobe Spectra device ($p < 0.0001$). The UK-based between-centre study of Kuo *et al.* (2015) reported packed RBC utilisation of 127 ml (31 units) for manual compared with 241 ml (55 units) for the Spectra Optia system ($p < 0.0001$) [6].

It has been proposed that using the depletion mode of the Spectra Optia device can reduce the volume of donor packed RBC required, and this was investigated by Quirolo *et al.* (2015) [11]. However, when weight was taken into account, there was no significant difference in RBC replacement volume between the modes, with standard RBCx requiring 14.7 ml/Kg (± 5.0 ml/Kg SD) compared with 17.2 ml/Kg (± 4.9 ml/Kg SD) for the depletion mode ($P \geq 0.05$). The study by Sarode *et al*. (2011) [12] reported that by implementing isovolemic haemodilution (IHD) using the Cobe Spectra system, significantly less packed RBC was used than standard apheresis (35.5 ± 4.1 mL/kg vs. 39.5 ± 4.6 mL/kg, 95% CI: 24.44 to 23.51, $p < 0.001$). However, as this was a

bespoke manual technique developed specifically for use in the Cobe Spectra system, the EAC does not consider this result to be applicable to the dedicated Spectra Optia depletion-exchange protocol.

In conclusion, the EAC considers the clinical evidence shows that the use of automated RBCx is associated with an increased use of replacement RBC. Although the extent of this increased need may vary, data from the UK study suggests that this requirement is approximately double that of manual RBCx. The EAC also considers that the company's claim "depletion-exchange protocol of the machine makes better use of donor blood as only the required fraction is used allowing the remaining blood components to be used in other patients" [1] does not have clinical evidence to support it.

BMI and growth in children

BMI and growth in children was not investigated in any of the comparative studies, but was the focus of a single-armed study using the Cobe Spectra system. The study by Bavle *et al.* (2014) used matched controls to investigate the impact of the Cobe Spectra system on child growth and peak height velocity [8]. However, the treatment both intervention and control groups received was poorly described and therefore it is not possible to draw firm conclusions from this study. Therefore the EAC considers that the company's claim that the Spectra Optia system results in "increased body mass index and growth in paediatric patients" has not been demonstrated by the available clinical evidence.

Alloimmunisation

Alloimmunisation was proposed by the company as an additional outcome measure in the statement of the decision problem (Table A1 in the company submission). The reason stated for this was that alloimmunisation is a known adverse effect of transfusion therapies and that the risk increases with increased exposure to donor blood. Alloimmunisation and blood unit exposure results were reported in three of the comparative studies and a further 10 studies presented in the company submission. Cabibbo *et al* (2005) stated that no patients developed clinically significant alloantibodies; with 1.8 units of RBCs used per procedure for manual exchange and 6.1 units of RBCs per apheresis procedure (three different apheresis systems, one being Cobe Spectra). Fasano *et al* (2015) reported an alloimmunisation rate of 0.50 per 100 units of blood for automated RBCx (device not specified) compared with 0.51 per 100 units of blood for partial manual exchange. The accompanying earlier study by Kaushal *et al* (2013) reported alloantibodies per 100 units as 0.55% for automated RBCx (device not specified) and 1.1% for partial manual exchange (p=0.57). The study of pregnant women by Asma *et al* (2015)

reported that 1/24 (4.1%) had RBC alloantibodies before automated RBCx began (using both Cobe Spectra and Spectra Optia). 4/24 (16.6%) became positive after exchange transfusion, as determined by indirect antigen testing. RBC antibody identification tests could not be performed in 3/24 (12.5%), but detected anti-D alloantibodies in 1 patient (4.1%). The authors did not confer any clinical significance upon these results.

Twelve of the 13 studies reporting alloimmunisation outcomes also specified that phenotyping and red cell antigen matching protocols were followed before the transfusions took place. Only Patel *et al* (2013) did not confirm this detail in their conference abstract [45]. Of the remaining studies reporting alloimmunisation data, only Kalff *et al* (2010) [9] reported any clinically significant findings, with 3/12 patients (23%) developing clinically significant alloantibodies with Cobe Spectra automated RBCx. However, a review of their transfusion data confirmed that these patients received antigen incompatible blood early in their treatment.

The EAC concluded that the evidence presented does not support the statement that the risk of alloimmunisation increases with increased exposure to donor blood. The most likely explanation is that the increased practice of limited and extended red cell antigen matching over time has improved the compatibility of donor blood in chronic transfusions for sickle cell disease.

Table 3.10. *Summary of EAC's critique on company's interpretation of clinical outcomes*.

	Clinical outcome (from scope)	**Direction of effect in clinical evidence compared with manual RBCx**	**Magnitude of effect in clinical evidence**	**Relation to company's claimed benefits***
Primary outcomes	HbS levels (%)	No consistent evidence of effect	N/A	Claim 4: increased efficiency resulting in reduced complications is not substantiated.
	Duration of procedure	Strong evidence of reduced duration	Spectra Optia: 1.5 to 2.5 hours Manual RBCx: 4 to 6 hours	Claim 2: substantiates claim that Spectra Optia results in shorter procedures, but not by magnitude of original claim.
	Frequency of treatment	Strong evidence of reduced frequency	Spectra Optia: 6 to 7 weeks Manual RCBx: 4 to 5 weeks	Claim 1: substantiates claim that Spectra Optia results in reduced frequency of treatment, but not by magnitude of original claim.
	Patient haematocrit	No evidence of difference	N/A	Claim 5: improved maintenance of haematocrit to prevent iron overloading is not substantiated.
	Iron overload and requirement for chelation therapy	Significant uncertainty whether ferritin levels are reduced	At least equivalent, magnitude of any reduction in ferritin unknown	Claim 3: reduced iron overload leading to reduced chelation therapy is not substantiated through reported changes in

	Clinical outcome (from scope)	Direction of effect in clinical evidence compared with manual RBCx	Magnitude of effect in clinical evidence	Relation to company's claimed benefits*
				ferritin levels.
	Clinical outcomes	None reported	N/A	Claim 4: improved outcomes, including reduced incidence of stroke, reduced frequency and severity of painful crises, and reduced incidence of acute chest syndrome, have not been substantiated. Claim 7: reduced complications leading to reduced hospitalisation has not been substantiated.
	Quality of life	Not reported	N/A	Claim 4: improvements in general quality of life have not been substantiated.
	Length of hospital stay	Not reported directly, but reduced hospital stay highly likely.	Not known	Claim 6: reduced hospital stay [outpatients] highly plausible.
	Staff time and staff group/grade	Not reported.	N/A	See Section 4.2.6.

	Clinical outcome (from scope)	Direction of effect in clinical evidence compared with manual RBCx	Magnitude of effect in clinical evidence	Relation to company's claimed benefits*
	Frequency of top up transfusion required to treat sickle cell complications	Unclear.	N/A	Does not affect claims.
Secondary outcomes	Ease of venous access, bruising and haematoma	Peripheral venous access more difficult using Spectra Optia system	Not known	Does not affect claims
	Device related adverse events	Weak evidence for increased catheter related complications in Spectra Optia, resulting in some patients transitioning to manual RBCx and some requiring hospital readmission	Dependent on site of vascular access, greater magnitude for femoral or implantable double lumen large-bore ports	Claim 7: reduced complications leading to reduced hospitalisations is refuted when femoral access is used for Spectra Optia.
	Hospital admissions	Possible reduction, but comparative data absent.	N/A	Claim 7: reduced complications leading to reduced hospitalisations unsubstantiated (lack of data).
	Donor blood usage	Strong evidence of increased	Some uncertainty, but probably double RBC requirement for	Claim 8: depletion –exchange protocol makes better use of donor blood is

	Clinical outcome (from scope)	Direction of effect in clinical evidence compared with manual RBCx	Magnitude of effect in clinical evidence	Relation to company's claimed benefits*
		requirement	Spectra Optia	unsubstantiated.
	BMI and growth in children	No direct evidence to support improved BMI and growth in children.	N/A	Claim 4: improved body mass index and growth in paediatric patients not substantiated.
	Alloimmunisation**	Consistent findings of no clinically significant difference in alloimmunisation rates between manual and automated RBCx.	No difference demonstrated when red cell antigen matching protocols are performed prior to transfusion.	N/A – no claim made in this regard.

* Claimed benefits are reported in the scope document [1]. For ease of reference, the EAC has numbered them in the order they appear (numbers 1 to 4 patient benefits and 5 to 8 healthcare system benefits).

** Alloimmunisation was added as a variation from scope in Table A1 in the company submission to address a perceived safety consideration

3.6.5 Subgroup analysis

Six subgroups were listed in the scope for specific consideration [1]. These were: children and adults at high risk of stroke; pregnant or breastfeeding women; patients with iron overload; patients with acute chest syndrome; patients with multi-organ failure; and children.

Children

Two of the comparative studies studied children exclusively. In the study by Dedeken *et al*. (2014) [3], 'older children' (median age at start of study 11.8 years) were investigated in a 'before and after' protocol. However, with no adult comparator group little information on treatment differences between adults and children was gained. This was similar for the study by Duclos *et al*. (2013) [4] which exclusively investigated children. Other studies have included mixed-age populations but have not reported disaggregated data. In this context, age might be considered a confounding variable because of differences in body mass and venous access.

The study by Quirolo *et al*. (2015) performed subgroup analysis on adults (n = 40) and children (age not defined, n = 20) [11]. This study found no significant differences between the groups except for the volume of replacement packed RBC (1449 ± 260 ml compared with 2118 ± 702 ml, $p < 0.05$). However, a significant difference was not seen when body mass was taken into account. This comparison was also confounded by the use of depletion exchange in the study.

Pregnancy

One study was identified that investigated the use of the Cobe Spectra system in pregnant women [56] (Section 3.4.5.). However, this study did not have an appropriate comparator, and as such is of limited value to the decision problem.

Patients with iron overload

No studies focussed specifically on patients with iron overload and compared them with those who were not. However, several studies included patients who were on chelation therapy, whilst some studies excluded patients who required chelation. In the case of the comparative studies that included ferritin as an outcome, three described a mixed population if people on chelating drugs and not on chelating drugs [2, 3, 6, 48], whilst one did not report chelation status [7]. However, none of these studies disaggregated the data or made direct subgroup comparisons between people receiving and not receiving chelation, so interpretation is limited.

Other subgroups

No studies were identified on patients with acute chest syndrome or patients with multi-organ failure. These patients would typically require emergency treatment which would technically put them out of scope (elective treatment only was considered).

Summary

In summary, the evidence for the Spectra Optia system in the specific subgroups identified in the scope was limited, with comparative data only being available for children compared with adults [11]. However, consideration of differences between these subgroups is important as it forms part of the basis of the economic submission (see section 4).

3.6.6 Clinical expert's feedback

Early during the process of critiquing the company submission, it became apparent to the EAC that there was a lack of good quality studies to demonstrate the clinical efficacy and safety of the Spectra Optia system (particularly comparative prospective studies). Partly because of this, the EAC canvassed the opinion of several clinical experts in the field of SCD and RBCx to gauge their opinions on the relative benefits of the Spectra Optia system. Out of 9 experts approached, 6 provided feedback on 11 structured questions set by the EAC and 1 ruled themselves out of acting as EAC expert, as they had already provided clinical input to the company during their evidence submission. Two experts failed to return a completed questionnaire. Not all of these experts had access or experience with all the methods of transfusions, and some experts were specialists in paediatrics, which in some cases made direct comparisons between technologies difficult. The full collated responses to these questions are reported in the EAC Correspondence Log, and a narrative summary of the answers to questions relating to outcomes in the scope follows.

An issue that was not adequately addressed in the published literature was how the interval between treatment cycles is derived. All the clinical experts who responded confirmed that this is determined by a combination of factors that depend on the patient's characteristics. The main factors that determined interval between treatments weres reported to be pre- and post-procedure HbS(%) levels and achievement of HbS targets, and patient symptoms. Patients are usually initiated on a set regimen which is then tailored according to measured response. Patient response depends on both the efficiency of the treating technology and their individual physiology (for instance their capacity to produce RBCs), hence there could be significant variation between patients. This suggests that the interval between treatments should

be partially related to the efficiency of achieving HbS targets, indeed this relationship was examined by Duclos *et al*. (2013), but although there appeared to be a trend, no significant association was reported [4]. However, the overall evidence was unequivocal that patients receiving automated RBCx are, on average, able to have longer treatment holidays than those receiving manual RBCx.

The EAC enquired about the clinical experts about the suitability of patients for top up and exchange transfusions, and was provided with clear indications on these. In summary, top up transfusions are preferred only when there is severe anaemia present and increasing the haematocrit is unlikely to cause risk of a vaso-occlusive event. In most other indications, RBCx is preferred (either manual or automated). One expert thought that increased access to RBCx would lead to its increased use, perhaps earlier in the disease process (although there were issues with staffing, training equipment availability, and venous access, particularly in young patients). One expert thought that RBCx would not be offered earlier in the disease process, but a consensus view was that automated RBCx would be preferred over manual RBCx if access was not an issue. Another expert advised that an exchange transfusion can be done first and then the HbS% kept low by continuing with a top up programme, and it is difficult to have numerous people on a regular manual exchange programme because it is very labour intensive.

The EAC enquired whether improvements in surrogate outcomes, in particular the proportion of HbS, would lead to improvements in the prevention of complications of SCD. The clinical advisors were unanimous that there was good evidence to show this, including evidence from controlled trials that improved control of target HbS levels can improve prevention of primary stroke [58, 59, 61], secondary stroke [62], and admission to hospital for SCD related crises [63]. However, whilst there is relatively good evidence that improved control of HbS results in good clinical outcomes, these studies were performed using mixed treatment regimens, and no evidence has been reported on differences between any incremental differences that may exist between manual and automated RBCx for these clinical outcomes. The studies that did compare HbS levels (absolute and achievement of target) were somewhat equivocal (Section 3.6.4).

An important claim made by the company was that the Spectra Optia system was more effective in reducing ferritin levels than manual RBCx, and thereby might enable more patients to avoid starting chelation or cease chelation if already iron overloaded. One expert reported that in theory both exchange methods were iron neutral, although practical difficulties might make manual RBCx less effective. Another expert, who uses only automated exchange in their centre, confirmed that they have certain experience of iron neutrality and

reduction in ferritin levels. One expert stated that patients were able to stop chelation after a period of being on automated RBCx, but had no experience to compare this with manual RBCx. Three experts thought that automated RBCx was generally more efficient, with a common reason being that less blood volume may be exchanged in practice during a manual exchange procedure, resulting in an intermediate iron-loading rate. One expert said that there was good observational data, including data from their practice that automated RBCx was superior to manual in improving surrogate iron content measurements, and speculated that this might be due to improved efficiency at removing old cells and preserving viability of new (transfused) cells. In summary, therefore, the experts were in agreement that automated RBCx with the Spectra Optia was likely to be beneficial in managing iron overload, although the mechanism for this was somewhat speculative.

The EAC received good information from the experts that manual RBCx was associated with a lot of procedural variation in practice. With regards to venous access, the experts confirmed that both manual and automated RBCx required adequate venous access to support two cannulas, which might be done peripherally or require a femoral line or use of ports. The success of achieving venous access was dependent on the skill of the phlebotomist (possibly aided by ultrasound) rather than dependent on the method of RBCx. One expert sometimes does a manual exchange transfusion when the automated exchange does not work (due to low flow rates). In such situations the manual procedure probably allows better control of how quickly the blood is removed from the patient (depending on how hard one pulls on the syringe). Two other respondents were unaware of any advantages of the Spectra Optia in maintaining venous lines through reduced pressure gradients.

The EAC enquired why there was a lack of good quality prospective studies comparing manual RBCx with automated methods such as the Spectra Optia. The general consensus was the lack of evidence could be due to a variety of factors including the relative rarity of the disease (especially the subset of severe disease requiring chronic exchange transfusion), lack of competitor products, and a general lack of funding from industry and charities to fund experimental studies. Importantly, all the experts who responded did not anticipate that future comparative trials between manual RBCx and automated RBCx would be justified because of a lack of clinical equipoise. That is, it would be deemed unacceptable or unethical to randomise patients to a manual RBCx arm because it is beyond clinical doubt that automated RBCx is at least as effective and offers clear additional benefits to the patient. This is discussed further in Sections 5 and 6.

When considered alone, the opinion of clinical experts is regarded as very low quality evidence. However, published evidence from clinical studies for the Spectra Optia system specifically, and RBCx in general, is scant and of poor quality, and in this context feedback from clinical experts can supplement this, and provide an impression of the device from the perspective of those that use it. A summary of the responses to key clinical questions is reported in Table 3.11 and full transcripts from the EAC questionnaire may be found in the EAC Correspondence Log.

Table 3.11. *Summary of feedback from clinical experts in relation to clinical outcomes and claimed benefits in scope.*

Clinical question	Feedback from clinical experts	Relation to claimed benefits or other aspects of scope*	EAC comment
How are intervals between cycles decided?	Combination of HbS levels and clinical symptoms. These may be affected by exchange method and a patient's individual physiology.	Claim 1: Automated red blood cell exchange using the Spectra Optia Apheresis System has a longer clinical effect than manual red blood cell exchange meaning that patients would require treatment only every 6–8 weeks in comparison with every 3–4 weeks.	Experts not asked to comment on time of intervals but how they are determined. The implication is Spectra Optia results in better control of HbS but this has not been detected in clinical studies.
Indications for top up or exchange transfusions?	Top ups suitable for treatment of anaemia where there is low risk of vaso-occlusive episodes (realtively low haemoglobin levels). Exchange indicated to more effectively reduce risk of vaso-occlusive episodes and reduce iron overloading. Automated exchange is generally preferred for most patients where it is available.	Top up transfusion as a comparator.	Top up transfusion has subtly different indications to exchange and cannot be considered a direct comparator.

What is relationship surrogate outcomes to clinical outcomes (especially proportion HbS)?	Good evidence to show improvements in HbS control reduces complications from HbS.	Claim 4: Increased efficiency of automated red blood cell exchange, in comparison with other transfusion methods 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….. Claim 7: Reduced complications from sickle cell disease leading to reduced hospitalisations and associated treatment.	Evidence from clinical studies on Spectra Optia improving HbS or other physiological parameters compared with manual RBCx is equivocal. No direct evidence of improved clinical outcomes of Spectra Optia relative to manual RBCx.
Relative effectiveness in reducing ferritin levels?	All experts who responded believed Spectra Optia was more “efficient” in reducing ferritin levels than manual RBCx. Mechanism unclear but likely to be due to procedural deficiencies in manual RBCx.	Claim 3: Treatment with the Spectra Optia Apheresis System could allow patients to reduce or cease iron chelation treatment due to reduced iron overloading. Claim 5: The Spectra Optia Apheresis System maintains haematocrit levels which prevents iron overloading.	Published evidence for reduced ferritin (or other measure of iron overload) has not been proven. Experts have not been asked to quantify this effect; however there is unanimous agreement that automated RBCx is beneficial in this regard.
Procedural variation and venous access?	Experts confirmed variation in manual RBCx practice. No difference reported in venous access and maintenance issues.	Secondary outcome: Ease of venous access, bruising and haematoma	No evidence from published literature or clinical experts on differences in venous access between Spectra Optia and manual RBCx.

Are future prospective, comparative studies warranted?	Experts unanimous that future studies are not needed because of lack of clinical equipoise.	N/A	Clinical experts are unanimous that overall Spectra Optia offers advantages over manual RBCx that would make further experimental research impractical or unethical.
* Claimed benefits listed from 1 to 8 in order they appear in scoping document.			

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3.7 Description of the adverse events reported by the company

Adverse events were reported by the company in sections 7.7.1 to 7.7.4 and with results from four additional studies presented in tables B10a to d of the company submission [41, 44, 46]. The EAC considered these reported adverse events as two separate and distinct issues: i) procedure-related complications common to all methods of blood transfusion for SCD (e.g. alloimmunisation [41, 44], thrombocytopenia [46]) and ii) device-related adverse events relating to the Spectra Optia or Cobe Spectra technology (e.g. catheter complications [7, 45], device failure).

Regarding Spectra Optia device failure, Table B11 in the company submission summarised 19 Medical Device Reports (MDRs) for red blood cell exchange procedures for the Manufacturer and User Facility Device Experience (MAUDE) regulatory process operated by the US Food and Drug Administration (FDA) in the period 1st July 2010 to 23rd May 2015. Additional reports were included in this table where the apheresis protocol was unknown, or faults were identified during maintenance, giving 77 in total. The company reported only one common device malfunction in this time period, in the Return Line Air Detector. Field safety notices (low risk) were issued worldwide by the manufacturer and these only related to the mononuclear cell collection protocols, not to any of the exchange protocols (including RBCx). The EAC considered the overall device failure rate insignificant (77/120,000 RBCx procedures completed), with no reported major patient injury or death being attributed to device failure.

Catheter complications were infrequently reported in the identified studies, limited to cases with femoral lines in adults [45] and large-bore double-lumen implantable port vascular access in children and adolescents [7]. Where these occurred, the patient tended to be transitioned to a manual red blood cell exchange procedure and no significant harm was reported.

More recent studies hypothesise that there may be an increased risk of alloimmunisation from increased units of red blood cell exposure with Spectra Optia but the effect has not been demonstrated to date, although no prospective studies have been reported.

The EAC therefore concludes with no significant safety concerns regarding adverse events for the Spectra Optia.

3.8 Description and critique of evidence synthesis and meta-analysis carried out by the company

In section 7.8 of their submission, the company stated that evidence synthesis (i.e. meta-analysis) was not appropriate because although the studies were of

similar designs (retrospective observational studies using routine data), the "range of outcomes, patient characteristics (where described) and the multiple units used do not permit useful meta-analysis to be conducted".

The EAC fully agrees with this conclusion. Compared with well-controlled experimental studies, non-randomised and observational studies, are likely to be subject to increased heterogeneity resulting from confounding and systematic bias, both within and between studies. For these reasons, it is essential that confounding factors are adequately identified and accounted for [64]. However, this was not the case for any of the included studies, and it was not possible to control for any confounding variables *post hoc* due to the poor standard of reporting.

3.9 Additional work carried out by the External Assessment Centre in relation to clinical evidence

It was apparent to the EAC from clinical expert feedback that a lack of access to automated RBCx was a significant operational barrier to realising the perceived patient and NHS system benefits of transitioning from manual exchange for chronic transfusion in SCD. The EAC therefore searched for additional information on these operational issues through the national programme of Haemoglobin Disorders Reviews, conducted by the West Midlands Quality Review Service (WMQRS).

The 2012-2013 Review of Adults used the Quality Standards for the programme as agreed by the UK Forum on Haemoglobin Disorders, and are based on the national guidance: 'Standards for the clinical care of adults and children with thalassaemia in the UK' [2005 and 2008] and 'Standards for the Clinical Care of Adults with Sickle Cell Disease in the UK' [2008].

The peer review of Barts Health NHS Trust, one of the largest centres in the UK, concluded that:

"Automated exchange transfusion was not available. In view of the large numbers of patients receiving manual exchange transfusion the provision of an automated service would have significant clinical and cost benefits."

By the 2014-16 Review of Adults and Children, the situation at this Trust had not improved:

"Automated RBCx facilities were not available at the Trust. The staff at The Royal London Hospital provided a manual exchange programme to an increasing number of patients. This arrangement further stretched available staffing resources."

The EAC therefore agrees with the clinical expert view that any procedural advantages of Spectra Optia in terms of efficiency and consistency are not being realised at present across the NHS; with the level of unmet need varying geographically.

3.10 Conclusions on the clinical evidence

The EAC considered that overall the company's clinical submission was of good quality with the company adequately answering the questions posed by the template. However, the EAC had reservations regarding some of the elements of the company submission, particularly in terms of the scope and the interpretation of the results. Therefore the EAC's conclusions were not fully concordant with that of the company.

In terms of the scope, the EAC accepted that the Cobe Spectra system had equivalent clinical efficacy to the Spectra Optia and therefore clinical studies on this system were admissible as evidence for the Spectra Optia system. It was also acknowledged that the Spectra Optia system was likely to have other benefits over the Cobe Spectra system in regards to safety, monitoring and convenience. The EAC also accepted that the depletion exchange protocol of the Spectra Optia system was within scope (although similar protocols exist for the Cobe Spectra system and manual exchange).

However, the EAC did not accept that simple or 'top up' RBC transfusions should be included in the scope. This was because national guidleines and clinical experts advise these are functionally and clinically non-equivalent interventions with different indications (depending on haemoglobin levels) and outcomes [26]. The EAC judged the company had not demonstrated that top up transfusions are commonly used instead of automated RBCx and hence it is not relevant to the decision problem, as the procedure could also be replaced by manual RBCx. The inclusion of top up transfusions by the company has important implications for the economic submission (Section 4).

The EAC considered that the company's literature search, although not fully transparent or comprehensive, was adequate. Although the EAC identified an additional four in scope studies not identified by the company through running additional searches, these were of methodological poor quality and did not add materially to the evidence base. The EAC was therefore satisfied that no negative studies of the Spectra Optia system had been withheld by the company (although undetected publication bias could not be ruled out).

The company critically appraised the identified studies using a tabulated checklist, which the EAC considered was an appropriate strategy. The company correctly reported the limitations of the evidence which in general was of poor quality in terms of study design, methodology, and reporting.

However, the company did not provide a narrative of the study limitations, and, in the opinion of the EAC, the company did not explicitly relate these limitations to the uncertainty they caused during the interpretation of results.

The EAC considered that overall the quality of evidence reported was very poor, with the large majority being retrospective observational studies. Only a minority of the studies were reported as full articles in peer-reviewed journals [2, 4, 8-12, 19, 20]. This was problematic because it is especially difficult to assess the quality of non-reviewed abstracts. All the studies were subject to issues with confounding which could not be resolved, had small sample sizes, and were subject to varying degrees of selection and reporting bias. However, the biggest issue was that most the studies were single-armed and thus direct comparisons of the intervention and comparator (with the limitations described) were simply not possible.

For this reason, the EAC focussed on the six studies that reported a comparison between the Cobe Spectra and Spectra Optia systems which were described as comparative [2-7], and one single-armed prospective study which was deemed to be of higher quality [11]. Four of the comparative studies were deemed to be of poor or very poor quality. The study by Cabibbo *et al*. (2005) [2] featured mixed interventions and full interpretation of the results was not possible. The study by Dedeken *et al*., reported as an abstract, (2014) [3] was a 'before and after study' in which all the participants received manual RBCx first; the EAC considered that this confounding factor severely limited interpretation of results. The study by Fasano *et al*., reported as an abstract [5] (2015) used inappropriate comparators. The study by Woods *et al*., reported as an abstract [7] (2014) was poorly reported and difficult to interpret.

The studies by Duclos *et al*. (2013) [4], published as a full article, and Kuo *et al*. (2015) [6], published as a letter, both compared the use of automated RBCx in one centre with manual RBCx in another. Despite their limitations, the EAC considered these studies were of higher quality and better reported than the other comparative studies. Additionally, the single armed prospective study by Quirolo (2015) [11] provided useful supplementary data including a comparison between standard and depletion modes of the Spectra Optia system.

The EAC considered the extent of how the outcomes reported in the scope [1] were answered by the included studies, and how these related to the company's claimed benefits. This was done in the context of the poor methodological quality of the studies causing considerable uncertainty, even in the better reported studies. A summary of the EAC's findings is presented in Table 3.12. The EAC considered that there was unequivocal evidence that,

compared with manual RBCx, 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 Spectra Optia). The EAC considered that the evidence on achieving HbS (%), haematocrit targets, and effect on iron overload was equivocal; that is the Spectra Optia system may provide benefit for these over manual RBCx, but this has not been adequately demonstrated. There was no comparative evidence reported on hospital admissions. There was 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 benefit of the Spectra Optia system on clinical and complication outcomes, such as stroke, painful crises, and acute chest syndrome.

Table 3.12. *Summary of evidence for outcomes reported in the scope.*

Evidence to support outcome	Outcomes (Spectra Optia relative to manual RBCx) *
Unequivocal (consistent evidence of effect and plausible)	Procedure duration (↓) [2-4, 6, 11-13] Procedure intervals (↑) [6, 12] Packed RBC required (↑) [3, 6, 9, 10, 12, 13]
Equivocal (evidence uncertain or conflicting)	HbS (%) and targets (↔) [3-7, 10, 12, 13, 65] Haematocrit targets (↔) [4, 6, 12, 13, 66] Iron overload (including ferritin) (↓) [2, 3, 5, 6]** Hospital admissions [9, 10] Alloimmunisation (↔) [5]
No evidence reported	Staff resource use Ease of venous access Quality of life BMI and growth in children

	Clinical outcomes (stroke, painful crises, acute chest syndrome)
* Reference cited for six comparative studies, and fully published and peer-reviewed single armed studies only. ** Most studies indicated trends for ferritin was downwards with automated RBCx but this was not always significant and results often confounded by methodology.	

The EAC canvassed the opinion of clinical experts on several key aspects of the decision problem in order to better understand their impression of the Spectra Optia's benefits over manual RBCx. All experts who responded were consistent with their feedback, which suggested that whilst there was no direct evidence the Spectra Optia system resulted in superior clinical outcomes compared with manual RBCx, it offered procedural advantages in terms of efficiency and consistency. In particular, the experts thought that the Spectra Optia system was likely to reduce chelation requirement. Overall, the experts considered automated RBCx offered enough advantages over manual RBCx to make further prospective, comparative studies untenable due to a lack of clinical equipoise.

4 Economic evidence

4.1 Published economic evidence

Critique of the company's search strategy

The company stated that no additional literature search was conducted for health economic studies, as they considered the clinical evidence search strategies should have identified any appropriate published economic analyses (submission, Section 8.1.1). As the company's clinical evidence search strategies were designed to search for studies on the device of interest, and were not restricted by study design or outcome, this was an appropriate decision. No reference was made in Section 8.1.1 to searches for unpublished economic analyses; it was therefore not possible to be certain if any of the activities used by the company to identify unpublished clinical evidence were also used to identify unpublished economic evidence, but it is possible this was the case. It is important to note that the strengths and limitations of the clinical evidence search methods (both in relation to search strategies and search sources), as referred to in Section 3.1, also apply to the identification of economic evidence.

The reporting of search methods was confused by the inclusion of partial search detail (rather than all, or none) in section 10.3 of the submission (submission, Section 10.3, Appendix 3: Search strategy for economic evidence). Just one MEDLINE search strategy was included (with line numbers which appear to be erroneous), although reference was made to other search sources. In addition, the search date in section 10.3 was reported as 03 June 2015. If this were the case, and only the 03 June searches were used to identify economic evidence, this would mean that the search for economic evidence was restricted to the initial, limited set of searches conducted, rather than the second extended literature search which was conducted on 09 and 10 June 2015. The lack of clarity in reporting meant it was not possible to be certain if all, or just some, of the clinical evidence searches were used. The company's statement that they considered the clinical evidence search strategies should have identified any appropriate published economic analyses, and the reference to additional search sources in section 10.3, would seem to indicate that the results of all clinical evidence searches were considered when identifying economic evidence. For the purpose of this critique it was assumed this was the case, and that the issue was just one of unclear methods reporting.

The information resources searched for clinical evidence included those indicated as a minimum requirement on the NICE Company's submission template for economic evidence searches: MEDLINE, MEDLINE In-Process,

Embase, Econlit and NHS EED. The range of databases was appropriate for identifying published economic evidence, though the addition of specialist economic sources such as Health Economic Evaluation Database (HEED) and the Cost-Effectiveness Analysis (CEA) Registry would have enhanced the search.

Appendix 10.3 indicated that the searches used for identification of economic evidence were conducted on 03 June 2015 (though as discussed above, it is likely the searches conducted on 09 and 10 of June were also used). The currency of the searches at the time of submission was therefore very good.

As the company did not carry out additional searches for economic evidence, there were no additional searches for the EAC to reproduce.

Included and excluded studies

The company included the seven studies that were identified in the clinical evidence section of the submission that also incorporated an economic analysis. These were the studies were:

- Adams *et al*. (1996) [21] compared the Cobe Spectra system with top up transfusions. This was published as a full peer reviewed study.
- Carrara *et al*. (2010) [22] was a single-armed study on manual RBCx, with hypothetical data on automated RBCx. This was reported as a conference abstract.
- Dedeken *et al*. (2014) [3] compared Spectra Optia with manual RBCx (before and after study). Reported as a conference abstract.
- Hilliard *et al*. (1998) [23] compared Cobe Spectra with top transfusions. This was published as a full peer reviewed study.
- Kalff *et al*. (2010) [9] was a single-armed study on the Cobe Spectra system. This was published as a full peer reviewed study.
- Masera *et al*. (2007) [10] was a single-armed study on the Cobe Spectra system. This was published as a full peer reviewed study.
- Sarode *et al*. (2011) [12] was a single-armed study on the Cobe Spectra system. This was published as a full peer reviewed study.

The EAC did not identify any additional economic studies relevant to the decision problem.

Overview of methodologies of all included economic studies

These studies have been reviewed in Section 3.5. In summary, these were retrospective studies of generally poor methodological and reporting quality. The reporting of the economic outcomes in these studies appears to have been performed on an *ad hoc* basis supplementary to the clinical analysis. Economic modelling was not used and resource identification was poorly reported and opaque. In general, only procedural costs were considered, although some studies also estimated the cost of chelation. None of the studies reported economic outcomes on clinical events. None of the studies were based in the UK so the generalisability to the NHS is uncertain.

Overview and critique of the company's critical appraisal for each study

The company critically appraised and summarised the results of each study in individual tables (Table C2 of the submission). The EAC considered this was appropriate since the studies were not of sufficient quality to undergo more rigorous critical appraisal using a checklist such as Drummond (2005) *et al*. [67]. The EAC agreed with the company that these studies added little to the decision problem and has therefore not appraised them further or attempted to extrapolate their results into NHS practice.

Does the company's review of economic evidence draw conclusions from the data available?

No, the company did not draw conclusions from the data available. In general, these studies indicated that the procedural costs of automatic RBCx may be more than manual RBCx or top up transfusions. This was consistent with the views of the company, who stated "we identified that per procedure costs were higher for automated RBCx with the Spectra Optia system than for the other types of regular transfusion" in Section 9.8.1 of the report. However, the effect of the addition of chelation and costs associated with other clinical events was explored in their *de novo* analysis.

4.2 De novo cost analysis

4.2.1 Company's literature search for parameters

Section 9.3.3 of the Company Submission template requires that the company provide a systematic search of relevant resource data for the NHS in England and include details of a search strategy. The company stated that they did not conduct a systematic search for resource data, and that resource use data were taken primarily from the published literature included in the clinical evidence, supplemented by other sources such as a Health Technology Assessment report and clinical advisers (submission, section 9.3.3). Costs were identified primarily from English national datasets. In section 10.4

(submission, section 10.4, Appendix 4: Resource identification, measurement and valuation) the company also indicated that where data were sparse or missing, studies that used “unidentified or alternative devices” were included, as were “key studies in top up transfusion”. No indication was given as to how these studies were identified. The reporting of search methods in the submission would have been strengthened by explicit and transparent reporting of how the studies referred to in section 10.4 were identified, even if the methods used were targeted and pragmatic. However, given the timeframes involved the EAC felt it would not have been feasible for the company to have performed a systematic search for the parameter values used in the submission. For similar reasons, no additional systematic literature searches for resource data were carried out by the EAC.

4.2.2 PICO analysis

The population (patients), technology (treatment intervention), comparators, and outcomes used in the model are described in the following sections.

Patients

The population included in the model was adults and paediatric patients with sickle cell disease requiring regular RBC transfusions and not limited to those requiring medium or long-term exchange transfusions, as defined in the scope.

In clinical practice, this represents a heterogeneous population, with patients with different characteristics and indications having different clinical needs and associated costs. To represent some of this case-mix, the company adopted 12 subgroups based on a mixture of age and clinical indication, and co-morbidity (degree of iron overload). The subgroups were:

- Children at high risk of primary stroke, with and without iron overload.
- Children being treated for prevention of complications of SCD, refractory to hydroxycarbamide or unable to take hydroxycarbamide, with and without iron overload.
- Adults being treated for prevention of complications of SCD, refractory to hydroxycarbamide or unable to take hydroxycarbamide, with and without iron overload.

Complications of SCD included secondary stroke and complications that might cause hospital admission such as painful crises, acute chest syndrome, or priapism. The degree of iron overload was divided into mild, moderate and

severe, according to serum ferritin levels. Thus there were eight scenarios described in children with two indications, and four in adults.

The company did not fully justify the choice of subgroups, but it appeared to be partly on the basis of the available clinical evidence to populate the model. However, there are some difficulties associated with the company's subgroup approach. Firstly, by subdividing the target population there is a risk that the already poor clinical evidence to inform parameter inputs into the model will be further 'diluted'. Many of the studies in the clinical evidence had mixed characteristics in terms of age and iron load or chelation status, and it was seldom possible to disaggregate the results. Secondly, the subgroup approach used dichotomised continuous scales, with no clear definitions on who constitutes a child or what constitutes moderate iron overload (for instance). There are greater similarities between a 12 year old child and a fully grown adult than with an infant. Thirdly, the outputs of the model are specific only to the subgroup investigated. This means that without detailed demographic information on the makeup of people with SCD in England, an overall estimate of cost expenditure per typical patient cannot be reported. These issues are discussed more fully later in the document.

Technology

The intervention in the *de novo* model was the Spectra Optia system for automatic RBCx, in either standard or depletion modes. As discussed in Section 2.3.2, the Cobe Spectra system was considered to be functionally equivalent to the Spectra Optia system in terms of efficacy, and so studies on this device were included. However, in the economic submission, studies on automated RBCx systems other than the Cobe Spectra or Spectra Optia systems were included. This was primarily when comparing automated RBCx systems with top up transfusions.

Comparator(s)

The *de novo* model has two comparators; these are manual RBCx and simple or 'top up' transfusions. Inclusion of the latter was justified by the assertion that use of automated RBCx rather than top up transfusion at an earlier stage in the patient's transfusion pathway could improve clinical outcomes and patient experience, whilst reducing iron chelation therapy costs, thereby reducing total costs.

Manual RBCx was consistent with the final scope [1], but the EAC considered that top up transfusions should be ruled out of scope for the reasons discussed in Section 2.3.4. Accordingly, although data from this comparator

have been analyzed by the EAC, it was with the reservation that it did not help answer the decision problem.

Outcomes

The economic model was effectively a costing model that did not quantify clinical outcomes. Four resource inputs described in the scope contributed to the cost inputs of the model [14], two of which had supporting evidence from clinical studies:

- Duration of exchange procedure (supported with evidence from clinical studies)
- Staff time and staff group/grade
- Frequency of top up transfusion required to treat sickle cell complications
- Donor blood usage (supported with evidence from clinical studies)

Results were presented as total aggregate modality costs..

4.2.3 Model structure and function

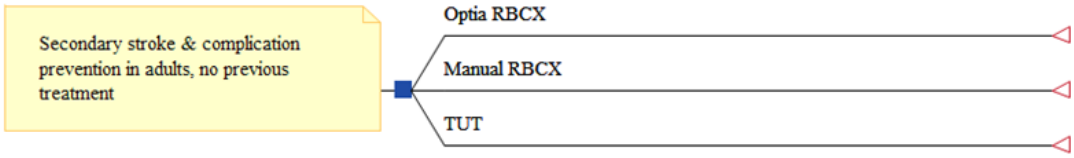
Software

The executable economic model provided to the EAC was written in TreeAge Pro (TreeAge Software, Inc). This is a dedicated economic software package frequently used for the construction and analysis of health economic models, and is approved by NICE [68].

Structure

This was a simple costing model which simulated the ‘average’ cost of the treatment of a patient with chronic SCD using one of three modalities; these were automated RBCx (Spectra Optia), manual RBCx, or top up transfusion. This structure resembled a decision tree but contained no clinical states or transition variables. Instead, each arm of the model was used as a costing algorithm. An example arm is shown in Figure 4.1. All the arms were essentially identical with the only differences being changes in the value and implementation of certain input parameters.

Figure 4.1. *Example scenario (adults, no iron overload) illustrating structure of model.*



The inputs which contributed to the final cost result were:

- Procedural costs. These included staffing costs, blood costs (packed RBC) and system costs (consumables only, capital and maintenance costs of device were not included).
- Hospital admission costs (for treatment of complications).
- Stroke costs.
- Chelation costs.

The costs were calculated in a variety of ways. For procedural costs (consumables, staff, and blood use), the unit cost per procedure was multiplied by the number of procedures per year and extrapolated over the time horizon of the model. For other costs, such as admission for complications, an average annual rate of occurrence was estimated and this was used to calculate average costs over the time horizon of the model. Secondary stroke cost was calculated using a one off event rate at the median time point in the model. Chelation costs were calculated using various assumptions on the iron load status of the patients in each arm of the model.

The model assumptions and estimation of clinical and cost parameters are discussed in Section 4.2.

Functionality of model

The model had limited functionality. All the scenarios shared the same structure and calculations, but some of the populating parameters could be changed to represent differences in the underlying population in terms of clinical status, chelation requirement, and costs associated with these. This could be done by manually overwriting variable values within the TreeAge model, and then re-running it. In addition, the EAC was able to extract the data and replicate the model in Microsoft Excel (see Section 4.3.1).

Time Horizon

The time horizon of the economic model was 5 years. The company reported that this was because “most clinical outcomes (stroke, hospital admissions, etc.) have been included as an event rate per year or per 5 year period”. The company claimed that this would have a conservative effect on the model because the benefits (such as stroke prevention) would be expected to accrue beyond the 5 year horizon. The EAC considered that this would probably be true but the clinical benefits in the shorter term would need to be shown first.

The EAC considered that 5 year time horizon was appropriate given the restrictions in the clinical evidence used to inform important parameters. The higher quality comparative studies generally collected data over shorter periods than this and further extrapolation would increase uncertainty.

Discounting

The company applied a discount rate on costs of 3.5%. This is standard practice for economic models submitted to NICE [68]. The discount was applied appropriately.

4.2.4 Model assumptions

In section 9.1.6 of the submission, the company provided a bulleted list of assumptions, with an accompanying justification for them. The EAC has independently critiqued the rationale for these assumptions in this section (grouped into categories). The values used in the model to support these assumptions are discussed further in Sections 4.2.5 and 4.2.6.

Patient pathways

> “There is no change of setting between each of the transfusion modalities. Each modality is provided by the same clinical service in secondary care and there are no differences in infrastructure requirements.”

The EAC agreed this was a reasonable assumption for the Spectra Optia device and manual exchange; each would be performed in the same facilities. However, the EAC also explored other commissioning options for the Spectra device (Section 5).

Moving from top up transfusion to an automated device may require the purchase of a vascular ultrasound device for insertion of central intravenous lines in the department at a cost of £30,000. (value provided in confidence).

The company assumed patients receive only one type of transfusion therapy over the time horizon of the model. This simplification is valid for the

comparison of manual and automated exchange but less realistic for patients receiving top up transfusions. This is because patients receiving top up transfusions may have different initial indications to those receiving exchange therapies and, should the clinical need arise (for instance because of iron overloading), the former may be switched to exchange transfusion (automated or manual depending on the facilities, see Figure 2.1), or partial exchange transfusions. However, the EAC appreciates there may be practical difficulties involved with access to full RBCx, for instance geographical location.

> "Patients are compliant with the prescribed treatment regimes."

The EAC considers this is a reasonable assumption considering the lack of data on patient compliance. The assumption is likely to be conservative because there is anecdotal evidence patients prefer automated RBCx over manual RBCx (see EAC Correspondence Log), which might be expected given the shorter procedure times.

Treatment procedure

> "The number and type of blood tests, before and after each transfusion procedure, are identical between modalities".

The EAC considered that this was valid for the comparison of automated and manual RBCx, but might not be for top up transfusions which has different indications. However, the cost effects of these tests on the overall pathway are slight (Section 4.3.2).

> "Haematologic targets for each procedure are independent of transfusion modality, i.e. post-procedure HbS, haematocrit and haemoglobin levels."

The EAC considered this assumption was valid when comparing automated and manual RBCx, which generally have the same haematocrit and HbS targets (typically 30%). However, such targets may not be adopted with top up transfusions and hence some tests may be omitted. This assumption did not have a material impact on the model.

> "Manual RBCx is conducted by a junior doctor (F1, F2 or registrar) or senior specialist haematology nurse (Band 7) and the procedure requires their full-time attention plus an additional clinician to assist (collect blood units, remove phlebotomised waste blood, check blood pressure, etc). This is modelled in the base case as 1.5 staff per patient for the duration of the procedure time."

There is no published evidence with which to base this assumption on, and clinical practice appears to vary (see summary of EAC Clinical Expert feedback in Table 3.11 and full transcripts in the EAC Correspondence Log). These values are considered further in Section 4.2.5.

> "Automated RBCx and TUT do not require the full-time attention of a clinician and can be conducted by a haematology nurse (Band 5). This is modelled in the base case as 1 and 0.5 nurses per patient respectively. These proportions are applied to the procedure times and an additional 30 minutes is added to each procedure for all three modalities for setting up the transfusion and removing the equipment afterwards."

There is no published evidence with which to base this assumption on, and clinical practice appears to vary (see EAC Correspondence Log). These values are considered further in sensitivity analysis Section 4.3.2.

> "Patients receiving automated RBCx do not preferentially require femoral or jugular central venous catheters (CVC) or implanted ports… [abridged]".

Automated RBCx is only suitable for people with adequate venous access, which rules out some patients (particularly younger children) from receiving the treatment [26]. In the study by Kuo *et al*. (2015), peripheral venous access was achieved in the majority of patients who received manual RBCx, but in only one patient who received Spectra Optia [6]. However, this may have been due to procedural differences between centres, or differences in the age of the patient, rather than differences in clinical requirement. A personal communication, provided in confidence, noted central venous access is required for most patients to undertake automated exchange transfusion and thus necessitated purchasing a vascular ultrasound device.

Thus limited evidence suggests this assumption may be unfounded, and there are operational differences between modalities with regards to venous access.

Chelation

> "All patients requiring chelation therapy are prescribed deferasirox (Exjade) rather than desferrioxamine mesilate (deferoxamine mesilate). This is the preferred medication (Cherry *et al* , 2012; Howard and Telfer, 2015) due primarily to its mode of administration (oral suspension rather than subcutaneous transfusion)."

The EAC accepted that deferasirox (Exjade) is likely to be used in clinical practice because of its route of administration (oral compared with subcutaneous for desferrioxamine mesilate). However, it is also considerably more expensive than desferrioxamine mesilate, and since the cost of the chelation is one of the main drivers of the model, this parameter should be subject to sensitivity analysis (Section 4.3.2).

> "Patients need for iron chelation therapy changes over time depending on their starting iron levels and the mode of transfusion… [abridged]"

The EAC agrees that top up transfusion, which is an iron positive therapy (increases systemic haemoglobin and iron), will in many cases, result in iron overload without the introduction of effective chelation

Differences between automated and manual exchange in reducing or stabilising serum ferritin has not been demonstrated in clinical studies. One clinical expert advised that the two methods should, in theory, be iron neutral (as both are isovolaemic) but added that problems with venous access may result in difficulty in ensuring equal amounts of red cells are exchanged [with the manual technique]. All experts advised automated exchange is more efficient, with two advising this view is informed from observations from their own patient data. No quantification of benefit was provided. Given the absence of robust published evidence (Section 3.6.4) there is considerable uncertainty on the magnitude of the relative benefit of automated exchange compared to manual exchange. This issue is discussed further in Section 4.2.5.

System costs

> "No training costs are included as the manufacturer provides initial and ongoing training included in the cost of purchase and maintenance."

Two experts noted that a barrier to take-up is training, including training new staff as existing trained staff leave the unit. Hence sites may not be aware that this activity is included in the cost base.

A major weakness with the company submission is the exclusion of capital costs (£52,052 per device) and maintenance costs (£4,572 per year) for the Spectra system. This issue is discussed in Sections 4.2.6 and the effect quantified in Section 4.5.

4.2.5 Clinical parameters and variables

Although the model did not include clinical states or transition probabilities as would be expected in a standard state transition model, some of the cost calculations did implement crude rate estimates which affected the final

costing outputs. Therefore The EAC has critiqued the company's estimates of clinical parameters in this section.

Requirement for chelation

An important aspect of the company's model was the patient's requirement for chelation treatment, which was estimated differently across the three transfusion modalities modelled. The main assumptions were as follows:

- In patients *without* iron overload at baseline and receiving treatment with the Spectra Optia system, no chelation would be required for the duration of the model. However, a proportion of patients receiving manual RBCx would require chelation, which was estimated as 10% after 24 months, 30% after 36 months, and 50% from 48 months onwards. These estimates were informed by results from Dedeken *et al* (2014) [3] and Cabibbo *et al* (2005) [2]. For those receiving top up transfusion, 90% of patients required chelation from 12 months onwards. This estimate was informed by data from The National Haemoglobinopathies Registry Report[34] , with the company noting the Registry identified an actual value of 75%; the 90% was justified because of data issues with the registry.

- In patients receiving manual RBCx or top up transfusion *with* iron overload at baseline, none would be able to cease chelation during the course of the model. However, a large proportion of those receiving treatment with the Spectra Optia system would experience a significant drop in their iron levels and be able to permanently cease chelation. The exact proportion depended on the initial iron overload status (mild, moderate, or severe, see Table C2.1, section 9.1.6). The derivation of these values is unclear but the company notes two clinical advisers, indicated that these estimates understated the reduction in iron chelation rates with the Spectra Optia system.

The EAC noted these assumptions were not based on the clinical evidence reported in the submission (as critiqued by the EAC in Section 3.6.4). Although there was some evidence from individual studies that the use of automated RBCx may reduce serum ferritin levels, the evidence base as a whole was equivocal with, for instance, in the abstract version of the comparative study regarded as relatively high quality by the EAC (Kuo *et al*., 2012) [48] there was no significant differences reported in ferritin trends between manual and automated RBCx in unchelated patients. The authors did report that automated RBCx was associated with less inter-patient variability however [48]. In contrast, the studies cited by the company for this

outcome were graded ‘poor’ for Dedeken *et al* (2014) [3] or ‘very poor’ for Cabibbo *et al* (2005) [2] by the EAC.

Additionally, there was no evidence that surrogate markers that might be expected to be related to iron overload (such as haematocrit or HbS proportions) were improved with automated RBCx.

The EAC reviewed the responses from the company’s clinical advisors but these did not appear to directly support the values used in the model. A limitation with these was advisors rarely had experience in all three transfusion methods. They were therefore unable to offer a comparative estimate with regards to the need for chelation in patients receiving automated or manual RBCx, or top up transfusions. In particular, there was a lack of feedback on the need for chelation with manual RBCx. Additionally, evidence from individual experts is principally applicable to their own practice and subject to recall bias.

In their discussion, the company stated “Our choice of these rates are somewhat arbitrary, but are consistent with the evidence and we consider them to be conservative with respect to expectations from clinicians who want to adopt automated RBCx”. The EAC considered that a more conservative base case would be to assume no difference between the chelation requirements of people receiving manual or automated RBCx. This would be consistent with the equivocal nature of the published evidence base. Moreover, in theory, as both methods involve isovolaemic replacement of blood components, they should both be iron neutral. Under this assumption patients with no iron overload at entry into the model and receiving manual RBCx should not develop overload. Those with existing iron overload should experience similar reductions in iron overload with continued chelation to those on the automated device. This is important because the cost of chelation is a key driver of the results (see Section 4.3.1).

For top up transfusions, the company discussed evidence from several studies that were not included in the clinical evidence section of the submission; these were the studies by Lee *et al*. (2006) and Adams *et al* (1998) [57, 58]. The EAC considered it was likely that using top up transfusions would result in iron overload but in clinical practice exchange options would be considered, rather than limiting the pathway to top up transfusions only (although there may be practical difficulties in achieving this). The EAC noted that the consequences of chronic iron overload on patient health and NHS resources had not been modelled.

The EAC's clinical experts were unanimous that automated RBCx provided benefits for reducing iron load compared with manual RBCx but they did not quantify the relative benefits (see EAC Correspondence Log).

Rate of hospital admissions

The parameter 'rate of hospital admissions' directly relates to the incidence of complications of SCD which requires hospital treatment (principally painful crises and acute chest syndrome). In the base case of their model, the company made the following assumptions for each treatment modality and indication:

- Spectra Optia system: 0.65 admissions per year, based on mean value (non-weighted) of three single armed studies of Cobe Spectra device by Kalff *et al*. (2004) [9], Masera *et al*. (2007) [70] and Pocock *et al*. (2004) [71]. The last study was not presented in clinical evidence section of submission and has not been critically appraised.

- Manual RBCx and top up transfusions: 1.1 admissions per year based on the studies of Webb *et al*. (2014) [42] and Wallace *et al*. (2014) [72] (neither study critically appraised in clinical evidence Section).

- Spectra Optia for primary stroke prevention in children: 0.1 admissions per year, data from Miller *et al*. (2001) [63] (study not presented in clinical evidence section of submission).

- Manual RBCx and top up transfusions for primary stroke prevention: 0.2 admissions per year (rationale for this unclear but stated to be based on Miller *et al*. (2001) [63]).

The EAC considered that no firm conclusions could be drawn from these which were:

- Non-comparative with low patient numbers.

- Retrospective and performed in a wide range of settings, in populations with different indications, and with mixed treatments. This, together with poor standards of reporting, made meaningful comparisons between the groups impossible.

- Not all were included in the company submission [63, 72, 73] or had been considered out of scope [42]. As noted at Section 4.1, the EAC questions the robustness of the search for resource use in manual and top up transfusions.

The EAC noted that the question of differences in re-admission rates between automated and manual RBCx had not been posed to the clinical experts, so the reasonableness of the company's estimates had not been verified as appropriate for the NHS setting.

In conclusion, the company estimated from the literature that using the Spectra Optia device could lead to an absolute reduction in emergency admissions of 0.45 admissions per year in adults and children requiring preventative treatment of complications, and 0.1 admissions per year in children requiring primary prevention of stroke. In relative terms, this would be a reduction in hospital admissions of around 40% and 50% respectively. The EAC judged the evidence to support the values used in the model for these parameters was not robust and there is a lot of uncertainty around them. Indeed there is a case for omitting this cost parameter from the model.

Stroke rate

The rate of stroke was not listed as a specific outcome in the scope and therefore did not feature in the clinical evidence section of the submission. The company noted that the Stroke Prevention Trial in Sickle Cell Anemia (STOP) trial found that regular transfusions (simple or exchange) were effective in preventing stoke in children at high risk, but did not compare treatment modalities [58, 59]. The company identified an additional study (Hulbert *et al*. (2006) comparing RBCx (manual or automatic) with top up transfusions which reported the outcome of secondary strokes [74].

The company reported that in the study of 11 children treated with RBCx for an acute stroke, none had a further stroke over the 5 years follow-up. Of the 18 children who had a stroke and received standard care (including top up transfusions), 7 had a second stroke. The company equated this to a stroke rate of 0.07 strokes per year (7 strokes over 90 patient years), and from this estimated that the secondary stroke rates for patients receiving Spectra Optia, manual RBCx, and top up transfusions were 0.0, 0.01, 0.07 respectively.

The EAC considered that this was a relatively small retrospective study that would be subject to sources of confounding and bias, and may not be generalizable to the UK. The study did not specify the Cobe Spectra or Spectra Optia systems as interventions and was technically out of scope because it focused on emergency treatment. It was unclear to the EAC how the company derived the figure of 0.01 strokes per year for manual RBCx as this data was not reported in the study. Finally, the EAC questioned the relevance of secondary strokes as an outcome for the populations modelled. The assumption implies all the patients modelled, except children requiring primary prevention, have had a primary stroke prior to entry into the model.

This assumption is not valid. Therefore the EAC concluded that there were grounds for excluding this parameter from the model.

Adverse events

The company did not include the cost of adverse events from transfusions in the *de novo* model, justifying this in their narrative. The company identified four sources of potential adverse effects which could affect the cost of transfusions being: mild-moderate reactions; haemolytic transfusion reactions; other adverse events; and alloimmunisation.

Mild-moderate reactions referred to common reactions associated with apheresis, including citrate reactions (reaction to anticoagulant drugs causing calcium deficiency) and vasovagal reactions (caused by hypovolaemia). These reactions are easily treated at low cost. Citrate reactions are specific to automated RBCx; however vasovagal reactions may occur with both automated and manual RBCx. Since the company was unable to identify data on the relative frequencies of these reactions between the two modalities, and because the costs are low, the company excluded these reactions in the model. The EAC agreed with this approach.

Haemolytic transfusion reactions are potentially serious or life-threatening reactions that require hospitalisation. Although potentially a large unit cost per patient affected, this reaction is comparatively rare and can occur with all transfusion modalities. As the company was unable to identify comparative data on the relative incidence of this reaction across modalities they opted to exclude it in their model; the EAC agreed with this approach.

'Other adverse events' listed by the company referred to bleeding events and catheter complications. There is conflicting evidence in the literature about issues with venous access with automated and manual RBCx (Section 3.7). However, the EAC agreed that these data were not sufficiently robust to include in the economic model.

The fourth potential adverse event specified by the company was alloimmunisation. The company concluded that the available evidence did not indicate that automated RBCx is associated with a higher rate of alloimmunisation than manual RBCx [5, 41, 44]. As the rate of alloimmunisation did not have a direct impact on modality costs, the company's opted to exclude alloimmunisation in the model. The EAC agreed with this decision.

Summary of clinical parameters and variables

A summary critique of the clinical parameters and variables used in the economic model is reported in Table 4.1.

Table 4.1. *Critique of the clinical parameters and variables used in the economic model*.

Clinical parameter/variable	Value used by company	How value was derived	EAC comment
Requirement for chelation in non-iron overloaded patients.	Automatic RBCx: 0% Manual RBCx: 10%, 30% and 50% at 24, 36, and 48 months Top up: 90% after 12 months.	Extrapolation from equivocal published clinical evidence and UK Registry data. Numerical values not based on specific research.	Automatic and manual RBCx are isovolaemic exchange methods that should in principle be iron neutral but experts indicate the automated exchange is superior in clinical practice, Important driver of cost model.
Iron overloaded patients stopping chelation with automatic RBCx	Mild overload: 50%, 100% at 12 and 24 months. Moderate overload: 5%, 15%, 30%, 50% at 12, 24, 36, and 48 months. Severe overload: 0%, 5%, 15%, and 30% at 12, 24, 36, and 48 months.	Trends for reduced chelation requirements have been seen in observational studies, and have been verified by clinical experts. Numerical values not based on specific research.	Important driver of cost model.

Clinical parameter/variable	Value used by company	How value was derived	EAC comment
Initiation of chelation therapy in patients receiving manual RBCx	In patients without initial iron overload. After 12 months 0%, after 24 months 10%, after 36 months 30% and after 48 months 50%. In patients with iron chelation: 80% at commencement and no change over time.	In patients without initial iron overload Extrapolation from equivocal published clinical evidence. Numerical values not based on specific research. Assumption of no change In patients with iron chelation at commencement is not clearly specified.	Important drivers in cost model.
Rate of hospital admissions (admissions per year)	In secondary prevention (adults and children): 0.65 (automated RBCx) and 1.1 (manual RBCx and top up) In primary prevention (children): 0.01 (automated RBCx) and 0.02 (manual RBCx and top up)	Mean (non-weighted) estimates from small non-comparative studies. No clinical input on plausibility.	Data highly extrapolated from equivocal evidence base. Large uncertainty regarding the plausibility and accuracy of these figures, no direct evidence automatic RBCx superior to manual RBCx.
Stroke rate	Automated RBCx: 0.00	Values from a single paper of a small retrospective study in emergency	Patient group in study is not appropriate. Stroke 'impossible' with

Clinical parameter/variable	Value used by company	How value was derived	EAC comment
(secondary stroke events per year)	Manual RBCx: 0.01 Top up: 0.07 [No difference in primary stroke rates assumed across the modalities.]	patients receiving mixed treatments. Unclear how value for manual RBCx was derived.	automated RBCx seems implausible. No evidence presented that automatic RBCx is superior to manual. Secondary stroke rate has been applied to entire population except children requiring primary prevention of stroke implying all adults have had a previous stroke.
<u>Adverse events</u>: Mild-moderate reactions Haemolytic transfusion reactions Bleeding and catheter complications	No values used in model	N/A	EAC agreed there was insufficient clinical evidence to describe incremental differences in adverse effect profiles across the modalities.

Clinical parameter/variable	Value used by company	How value was derived	EAC comment
Alloimmunisation			

4.2.6 Resource identification, measurement and valuation

Procedure time

Procedure time directly relates to the procedure cost through different usage of staff resources and was measured in several of the published studies. Reduced procedure time may also improve patient experience although this was not explored in the model. The company calculated a mean value from data derived from both comparative and single armed studies (of automated RBCx only) in children and adults. It was not clear if these values were weighted according to the size of the studies, nor how the values for manual RBCx and top up transfusions were derived.

The company calculated times of 110, 245, and 300 minutes and 86, 245 and 180 minutes for adults and children receiving Spectra Optia, manual RBCx and top up transfusion respectively. The EAC was unable to replicate these values using the data cited. Although the values for adults appeared reasonably consistent with the values reported for Spectra Optia and manual RBCx in the comparative study of Kuo *et al*. (2015) [6], the EAC considered that the procedural time for manual RBCx in children, which was based on the before and after study by Dedeken et al. (2014) [3], was the same as for adults which was unrealistic.

Number of procedures per year

The number of procedures per year (for automated and manual RBCx) was reported, or could be calculated from, the comparative studies of Dedeken *et al*. (2014) [3] and Kuo *et al*. (2015) [6]. Although it is not clear how the company selected the values of 8.5, 12 and 13 procedures per year for automated RBCx, manual RBCx and top up transfusions respectively, these appear to be consistent with the comparative studies.

Number of RBC units used per procedure

The number of RBC units used per procedure was a measured outcome in several comparative and single-armed studies. The company stated that they used mean values from these studies but it was not clear if these values were appropriately weighted. The company adopted the values of 7, 4 and 2 units per procedure in adults receiving automated RBCx, manual RBCx and top up transfusions respectively and corresponding values of 5, 4, 2 units in children. It was unclear to the EAC why the units for manual RBCx and top up transfusions were not reduced for children given the study by Quirolo *et al*. (2015) [11], noted a positive association between units required and body mass. By not reducing the units used in children there is a tendency of bias

against top up transfusions and manual RBCx in the base case for these groups.

Number of staff per patient and staff grade

The number and grade of staff was not reported in any of the clinical studies so the company relied on estimates from their clinical advisors. From this, the company estimated that the staff ratio would be 1.0, 1.5, and 0.5 for automated RBCx, manual RBCx and top up transfusions respectively. The company also assumed that manual RBCx would require a higher staff grade (band 7 nurse or junior doctor) than automated RBCx or top up transfusions (band 5 nurse). These bands were consistent with those advised by the one EAC clinical expert identifying nursing grades by modality.

The EAC considered that the rationale and values adopted by the company were reasonable and could reflect real-life practice; however, it was noted that clinical practice is highly variable and subject to material uncertainty. The cost of phlebotomists was also not factored in, although it is likely that this would be similar for both automated and manual RBCx. Staff costs were derived from the Unit Costs of Health and Social Care (PSSRU) 2014 [75], which was considered appropriate by the EAC.

Cost of stroke

For the cost of stroke, the company identified a National Institute for Health Research (NIHR) funded Health Technology Assessment by Cherry *et al*. (2012), which examined the clinical effectiveness and cost-effectiveness of primary stroke prevention in children with sickle cell disease [60]. In this model, stroke was represented as an acute phase lasting 3 months associated with a one-off cost, and an ongoing phase with an associated quarterly cost. In the base case, the company applied this as a one-off cost at the halfway point in the model (2.5 years); this assumed the risk of stroke was independent of time in the model. After adjusting for both inflation and discounting, the company introduced a cost of stroke of £21,807 for both adults and children requiring secondary prevention of crises; children requiring primary prevention of stroke had no possibility of having a stroke (primary or secondary) in the model.

The EAC considered that the selection of costs from just one source, bring a relevant UK-based health technology assessment was acceptable, given time pressures. However, the company's application of these data was somewhat simplistic and had the following shortcomings in that the Health Technology Assessment was:

- Concerned with primary stroke prevention, but in the company's model only secondary stroke prevention was included. The costs of primary and secondary stroke are unlikely to be equivalent. Additionally, the company's model implied all people receiving transfusion treatments for secondary prevention of complications would have had a prior stroke, which appears unrealistic.

- Set in a population consisting exclusively of children, but the company extrapolated the cost data to include adults. It is unlikely the costs of stroke in adults and children with sickle cell disease are the same.

However, of more concern to the EAC were the underlying assumptions concerning the incidence of stroke, whereby it was assumed, for instance, that treatment with Spectra Optia was 100% effective at preventing stroke (Section 4.2.4). It was noted that although the company used sensitivity analysis to test the effect of cost and timing of stroke (Section 4.3.2), this underlying assumption was not adequately challenged.

Cost of hospital admissions

Modelled hospital admissions included episodes of painful crises and acute chest syndrome (ACS), with stroke being treated separately. The company derived these costs from NHS Reference Cost data (Table C5.3), for patients with sickle-cell anaemia with crisis. The company calculated a mean cost per episode of £1,354, a value reasonably consistent with the midpoint of the cost of a pain crisis and ACS adopted in the Health Technology Assessment by Cherry *et al*. (2012) [60].

The EAC agreed broadly with the methodology used to calculate the cost of an acute episode requiring hospital admission. However, the EAC had reservations on the validity of the estimated rates of hospital admissions following treatment with each modality (Section 4.2.4).

Cost of chelation

The company calculated their own values for the cost of chelation rather than adopt the value estimated by Cherry *et al*. (2012) because this was for children only. The EAC agreed with this approach given the cost of chelation medication is based on body weight.

The company assumed that the drug deferasirox (Exjade) would be used exclusively to perform chelation, and cited that "clinical preference" was for this drug over the other drug licensed for this use, desferrioxamine. However, data from the National Haemoglobinopathy Registry Report 2013/14 [34] indicates that deferasirox accounts for about 70% of iron chelation therapies.

This is important because deferasirox is substantially more expensive than desferrioxamine before administration costs are considered. Given this, the company could usefully have undertaken a sensitivity analysis on use of desferrioxamine in around 30% of patients.

The company calculated the cost of chelation with deferasirox using unit costs from the British National Formulary (2015) [76] (Table C5.4 of the company submission) and added in monitoring costs from the Health Technology Assessment by Cherry *et al*. (2012) [60], which the EAC deemed was reasonable. This resulted in a mean chelation cost of £9,954 for children and £21,022 for adults.

The EAC considered that the estimates of chelation costs used by the company had the following limitations:

- As described by the company, the effects of titration on the costs of chelation were not included which would likely lead to an overestimate in the required drug use.

- Chelation costs did not differ according to the degree of iron overload whereas, in clinical practice, it is likely that doses would be individually titrated and adjusted according to response [26]. However, this was explored in the sensitivity analysis (Section 4.3.2).

- As discussed, it was assumed that the more expensive drug deferasirox would be used solely instead of a more realistic assumption of 70%/30% between deferasirox and the cheaper drug desferrioxamine.

The EAC also considered there were serious limitations in the company's estimate of the clinical benefit of the Spectra Optia compared to the other modalities in terms of need for chelation. These are described in Section 4.2.4.

A further limitation was the assumption that iron overloading only impacted on medication costs. In practice diagnoses and monitoring is likely to require MRIs and regular blood tests; use of these medicines may also give rise to side effects which require to be managed. Moreover, poor control may result in additional management costs related to liver and spleen function. Hence more efficient prevention of iron overload could deliver substantial cost savings in the longer term (as well as improve quality of life) (Section 4.4).

Cost of consumables

The company included an additional cost of system consumables for the Spectra Optia of £167.84 (pre discounts), the cost of the Spectra Optia exchange set, which is additional to consumables used by other techniques (Section 9.3.5). The costs of the Astotube with injection port (£4.37 each) and ACD-A anticoagulant (750 ml) (£4.78 each) are used by all modalities and were correctly excluded from the model.

The main consumable cost for all transfusion modalities was for packed RBC. The company used a unit cost of £120 per pack, being a reference price from NHS Blood and Tissue Services (NHSBT). The EAC has confirmed a unit cost of £120.00 for packed RBCs as of September 2013 [69].

Technology costs

In Section 9.3.5 of the submission, the company listed the capital costs and annual service charges associated with the Spectra Optia system which were:

- Spectra Optia device: £45,351.60
- RBCx/RBC depletion software: £6,700.85
- Service charge: £4,572 per year

These costs were not included in the base case but were included in sensitivity analyses. The justification for this omission was stated in Section 9.5.11 of the company submission, being that the Spectra Optia system is a multi-purpose device which can be used for more than just automated RBCx. The company estimated the capacity of one system would exceed forecast demand at even the largest treatment centres managing 40 to 60 SCD patients on long term transfusion programmes. Hence haematology departments purchasing a Spectra Optia system would have spare capacity, allowing the device to be used for functions such as plasma exchange and stem cell harvesting.

The EAC judges this approach is not appropriate and the preferred approach is discussed in Section 4.3.3.

Summary of resources and costs used in model

A summary of the resources identified and costs used is reported in Table 4.2.

Table 4.2. *Resources and costs used in the model.*

Resource identified	Value used by company (baseline)	How value was derived	EAC comment
Procedure times (minute)	Adults Spectra Optia 110, manual RBCx 245, top up transfusions 300 Children Spectra Optia 86, manual RBCx 245, top up transfusions 180	Mean of several comparative and single armed (automated RBCx only) studies.	Evidence from clinical studies suggests significant reductions in procedure times. Company's estimates appear to be consistent with a comparative study in adults [6] but time of manual RBCx in children not reduced which was not realistic.
Number of procedures per year	Spectra Optia 8.5, manual RBCx 12, top up transfusions 13	Mean value from clinical studies supplemented with evidence from clinical advisors.	Evidence from clinical studies supports significantly increased intervals between procedures with Spectra Optia. This estimate consistent with evidence from two comparative studies [3, 6].
Number of packed RBCs per procedure	Adults Spectra Optia 7, manual RBCx 4, top up transfusions 2 Children Spectra Optia 5, manual RBCx 4, top up transfusions 2	Mean value from several comparative and single-armed studies.	Evidence form clinical studies supports significantly increased requirement for packed RBCs with Spectra Optia. The value adopted by the company for adults looks reasonable; however, the incremental difference between requirements in children appears too small and a potential bias.

Resource identified	Value used by company (baseline)	How value was derived	EAC comment
Number of staff per patient and staff grade	Spectra Optia 1.0 (grade 5), manual RBCx 1.5 (highly qualified), top up transfusions 0.5 (grade 5)	Estimates from clinical advisors.	Company's estimates for staff requirement realistic although clinical practice likely to vary substantially. Staff need specialist training for automated apheresis and qualified phlebotomist required for venous access.
Cost of stroke	One off cost of £21,807 at 2.5 years	Estimate from Cherry *et al*. (2012) [60]	Estimate was for an aggregated cost of primary stroke in children, but was extrapolated to secondary stroke in adults. No mortality rate.
Cost of hospital admissions	Mean hospital cost £1,354 (range £423 to £3,832)	Estimate from NHS reference cost data related to sickle cell inpatient stay with complication and comorbidity (HRG reference codes SA36A, SA36B and SA36C).	Cost estimates reflect a heterogeneous population of mixed characteristics (children and adults), indications (painful crises, acute chest syndrome) and treatments but excludes cost for those admitted without complications
Cost of chelation (per year)	Adults: £21,022 Children: £9,954	Drug costs calculated from drug regimens applying BNF unit prices and estimated body weights. Monitoring costs added from Cherry *et al*. (2012) [60]	Dosing regimen not adjusted for severity of iron overload. Monitoring costs in Cherry for children only and applied to adults. Chelating drug use assumed to be 100% deferasirox; desferrioxamine not included in model, despite 30% market share from Registry [12]

Resource identified	Value used by company (baseline)	How value was derived	EAC comment
Additional cost of consumables	Spectra Optia: £167.84 (Spectra Optia exchange set) Manual RBCx and top up transfusions: no cost	Information from manufacturer.	Cost of consumables other than Spectra Optia exchange set assumed to common across modalities
Cost of blood	£120 per unit packed RBC (all modalities.	Information from NHS Blood and Tissue Services.	Cost verified by EAC [69].
Cost of technologies	Capital cost and maintenance contract of Spectra Optia not included in base case results. Manual RBCx and top up transfusions: no such costs.	Pricing information from manufacturer	Capital costs of Spectra Optia should be included in model.

4.2.7 Sensitivity analysis

In their base case analysis, the company included 12 subgroups. In Section 9.4.1 of the submission, the company reported that they performed an additional 8 univariate deterministic analyses for each subgroup. These tested sensitivities to stroke timing and severity, hospital admissions, cost of medication, staff grades, staff ratios, red blood cell 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 performed to inform when the modality orderings changed.

The company stated the ranges adopted were informed by values taken from published clinical evidence, clinical advisers, manufacturer and reference sources.

The company also conducted scenario sensitivity analysis for four scenarios:

- Use of depletion exchange protocol in Spectra Optia, resulting in a reduction in the number of packed red blood cell units used in automated RBCx by one.
- Mild iron overload with low chelation costs.
- Severe iron overload with high chelation costs.
- Increased rate of patients ceasing chelation therapy for moderate and severe iron overload when receiving automated RBCx.

The EAC's concern about the selection of some key parameters and the values attributed in the central case are replicated in respect of the values adopted in the sensitivity analyses. For example:

- Inclusion of secondary strokes
- Relative benefit attributed to the Spectra Optia system for hospital admissions
- Limited benefit of adopting manual RBCx for those with iron overload, with numbers on chelation dropping from 90% to 80%. For patients with no iron overload at model entry, 50% of those allocated to manual RBCx are assumed to require chelation at 2 years.
- Exclusion of desferrioxamine from cost of chelation therapy.

- Exclusion of costs other than medication to manage iron overload.

The justification for the parameters chosen for deterministic and scenario sensitivity analysis were not always clearly stated; for example the rate of hospital admissions and strokes were varied by +/- 50%. However, given the uncertainty in the base case values an arbitrary choice of ranges for the sensitivity analyses is perhaps inevitable.

According to the company, probabilistic sensitivity analysis was not undertaken partly due to time constraints and the extensive subgroup and deterministic sensitivity analyses performed. Whilst the EAC notes that the quality of the primary data was of insufficient quality to inform probabilistic distributions, the EAC did not consider the justification given by the company to be valid.

Results from the sensitivity analysis are critiqued in Section 4.3.2.

4.3 Results of de novo cost analysis

4.3.1 Base case results

Model replication and validation

The EAC validated the cost calculations employed by the company by independently replicating its model in Microsoft Excel. The company's base case results could be perfectly replicated in the majority of scenarios. However, in order to accurately replicate the results for those patients using top up transfusions who entered the model with no iron overload a slight adjustment to the proportion of patients undergoing chelation therapy had to be made (90.03% used rather than 90.00%). Therefore, no substantive errors were identified within the company's base case calculations.

Base-case analysis results

The base-case results were reported for 12 patient subgroups for each modality. The subgroups were based on patient characteristics (children or adults), indication (secondary prevention of crises or primary prevention of stroke [children only]), and iron overload status (not overloaded, mild, moderate, or severe). Therefore a single value answering the question whether adoption of the Spectra Optia device would be cost saving if adopted for treatment of all clinically indicated people with SCD could not be determined.

The company reported the absolute value of the base case analysis in Table C11 of the submission. The absolute costs of treatment of SCD over the 5-year time horizon varied from £34,538 for Spectra Optia in patients with no overload, to £128,670 for manual

RBCx with overload. For patients receiving treatment with the Spectra Optia device, absolute costs of treatment increased according to their 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 receiving manual RBCx or top up transfusions. This was because in the base case, patients receiving these modalities did not alter their iron overload status and the regimen used for chelation was not related to severity of overload.

The differences in costs between Spectra Optia and manual RBCx or automated RBCx was reported in Table C11.1 of the company submission. This data showed showed that the Spectra Optia system was always cost saving compared with manual RBCx, with savings over 5 years ranging from £360 for adult patients with severe overload, to £52,516 per adult patient with mild iron overload. However, Spectra Optia was more expensive than top up transfusions in patients with moderate or severe overload. The reasons for this were because as chelation requirement increased, other factors such as cost of consumables and requirement for packed red blood cell units became more significant in the costing calculations in patients receiving Spectra Optia. In the case of patients receiving top up transfusions, the lower procedural costs outweighed increased chelation costs in these scenarios.

The company provided a breakdown of costs in patients without overload in Table C12a of the submission. It can be seen that the cost of chelation is a substantial component of the overall costs particularly in patients receiving top up transfusions where these account for 70% of the costs for adults (90% of these patients are assumed to require chelation after 1 year). For patients receiving manual RBCx, staffing costs are higher than the alternative treatments, and for patients receiving Spectra Optia the requirement for packed RBCis the largest cost component (almost 70% of total cost).

The cost of hospital admissions was lowest in patients receiving treatment with Spectra Optia but differences were under £3,000 so this was not a major cost driver. Similarly the cost impact from the inclusion of strokes across the modalities was low (maximum of about £1,500 over the five years) due to the low absolute incidence rates used for all modalities.

The company reported the cost of chelation and total costs in patients entering the model with iron overload in Table C12b of the submission. As expected, the cost of chelation was not related to severity in patients receiving manual RBCx or top transfusions, but increased according to severity in patients receiving Spectra Optia. The chelation costs were a higher proportion of total costs in patients receiving top up transfusions than other modalities, for instance in adults with mild overload and

receiving top transfusions, this cost represented 74% of costs, compared with 61% for manual RBCx, and 37% for Spectra Optia.

EAC summary of base case results

The company's provided an economic model based on 12 clinical subgroups. Although the model could not provide one single answer to whether the Spectra Optia would be cost saving if adopted into NHS England, the system was reported as being cost-saving in the subgroups with no iron overload or mild iron overload at entry into the model. For patients with moderate or severe iron overload at entry the Spectra Optia had slightly higher costs than top up transfusions, but was always cost saving compared to manual RBCx. Thus to answer the decision problem defined in the scope the company's results indicate automated transfusions were always cost saving compared to manual RBCx.

However, the EAC has several concerns regarding the model. These include:

- The assumptions and estimations made regarding clinical parameters, in particular the benefit from the Spectra Optia for chelation usage, rate of stroke and hospital readmission.
- The underestimate of the cost of iron overload management.
- The exclusion of capital and maintenance costs for the Spectra Optia system.

These issues are discussed further in Section 4.4.

4.3.2 Sensitivity analysis results

Validation of results

Because of the large number of subgroups, sensitivity analyses yielded a large volume of results. The EAC used the Excel spreadsheet to replicate the company's sensitivity analysis results. On the whole, both the univariate and multi-way analyses could be accurately validated. However, in a small proportion of the analyses, the EAC generated results that differed to the company. These are now listed with the table number in the company submission provided:

- Children – no iron overload (Table C14.1, submission): Number of RBC units used per automated procedure. EAC ranking showed TUT rather than automated to be the most expensive method, i.e. EAC ranking of 1. Manual; 2. Automated; 3. TUT.

- Adults – moderate iron overload (Table C14.3, submission): Number of manual procedures per year. EAC agreed with threshold and ranking, but found the cost of automated RBCx to be £119,779.

- Children, secondary prevention – moderate iron overload (Table C14.3, submission): “Greater than” signs are missing for five of the threshold values. However, the EAC agrees with the threshold values, value of automated RBCx and ranking.

- Children, secondary prevention – moderate iron overload (Table C14.3, submission): Number of RBC units used per automated RBCx procedure. EAC agrees with threshold value and ranking, but calculated a value of automated RBCx of £67,197.

- Children, primary prevention – moderate iron overload (Table C14.3, submission): Cost of chelation therapy. EAC agrees with threshold value and ranking, but calculated a value of automated RBCx of £91,734.

- Children, secondary prevention – severe iron overload (Table C14.4, submission): for all analyses the EAC generated a cost of automated RBCx of £76,003.

- Children, secondary prevention – severe iron overload (Table C14.4, submission): Number of manual RBCx procedures per year. The EAC agreed with the threshold value, but found manual exchange rather than TUT to be the cheapest method of exchange, i.e. EAC ranking of 1.Manual; 2. TUT; 3. Automated.

- Adults – severe overload, high chelation scenario (Table C14.5, submission): EAC results for all exchange methods varied slightly to the company’s results (EAC results: Optia = £185,200; Manual = £184,406; TUT = £181,598). This difference was less than £80 for each method and had no impact on the ranking of exchange methods.

Sensitivity analysis results

Univariate analysis

In Section 9.5.6 of the submission, the company reported that they used tornado analysis to determine which costs inputs the model was most sensitive to in patients without iron overload and these were:

- Number of RBC units used in automated RBCx
- Number of manual RBCx procedures per year
- Number of automated RBCx procedures per years
- Cost of a hospital admission, or chelation costs.

The company tabulated these key sensitivity analyses according to iron overload status in Tables C14.1 to C14.2, which listed scenarios (according to threshold analysis) where Spectra Optia was *not* the cheapest option. In Tables C14.3 to C14.4 scenarios were listed where top up transfusion was not the least costly option.

The company provided a narrative to discuss the results from these tables which can be summarised thus:

- For patients without overload, manual RBCx became the least costly modality in some scenarios where procedure costs of automated RBCx increased (mainly due to requirement of packed RBC) or intervals between manual procedures increased. Top up transfusions became least costly option if chelation costs were substantially reduced.
- For patients with mild overload, top up transfusions became the least costly option if large decreases in chelation costs or the requirement of Spectra Optia for packed RBCgreatly increased.
- For patients with moderate iron overload, top up transfusions were the least costly option in the base cases. Spectra Optia became the cheapest modality if the cost of chelation therapy was substantially increased or automated procedure costs were reduced. In this analysis, the company also calculated that Spectra Optia might become the least cost option if the rate of hospital admissions or the cost of admission or stroke were substantially increased.
- For patients with severe iron overload, top up transfusions were the least costly option in the base cases. The cost rankings of treatments were altered using alternative number of procedures (reducing the frequency of manual or automated procedures could promote either modality to be least cost) or five times higher stroke costs which ranked the automated option as cost saving.

Note as patients with no iron overload receiving automated RBCx do not have any chelation costs, increasing chelation costs only increases the difference between the modalities

Multivariate sensitivity analysis (scenarios)

In Section 9.5.7 of the submission the company reported on four additional scenarios; the company did not offer a rationale for why these were specifically selected.

In the first scenario, the company calculated the potential savings of reducing the requirement for packed RBCwith the Spectra Optia system by using the exchange-depletion mode. The company's calculated this could lead to savings of £4,766 per year; the EAC agreed this calculation was correct.

The assertion that using the exchange-depletion mode of the Spectra Optia system could lead to saving of one unit of RBCper procedure was mainly based on the study by Quirolo *et al*. (2015). This used subgroup analysis to compare patients who had received the depletion-exchange mode with those who had received standard exchange [11]. This study reported that 2,016 ml (± 729 ml [SD]) of packed RBCwere required for standard RBCx and 1,562 ml (± 281 ml) were required for depletion exchange. Whilst this was a significant reduction ($p < 0.05$) the authors reported that a unit's saving would only have been made in 3 of the 16 cases of depletion exchange. Given that depletion-exchange can only be used in patients who have adequate pre-procedure haematocrit, it was unclear if this saving could be realised in clinical practice. In the clinical evidence section of their submission, the company also cited the study by Sarode et al. (2011) [12] as showing that depletion-exchange can significantly reduce donor blood usage. However, as this study used manual IHD in the Cobe Spectra system, the EAC considered it was not relevant to the dedicated depletion-exchange protocol of the Spectra Optia system.

In the second and third scenarios (Table C14.5), the company described the clinical situation where the dosing regimen of chelation drugs was related to the severity of iron overload, such that people with mild overload received a low-dose regimen and people with severe overload received a high-dose regimen. The company calculated that for people with mild iron overload, top up transfusions and automatic RBCx had similar costs, with manual RBCx having the highest costs. For people with severe overload, results assuming increased doses of chelation drugs always ranked top up transfusions as the cheapest and manual RBCx as the most expensive. The EAC considered the premise of these scenarios as reasonable and the results self-explanatory.

For the fourth scenario (Table C14.6), the company assumed that cessation of chelation would proceed more rapidly if the patient received Spectra Optia. In this case, the Spectra Optia was cost saving in all the scenarios presented except for children requiring primary stroke prevention with severe iron overload, where top up transfusion had similar costs to the Spectra system. The EAC considered that it was clear that by

adjusting the chelation requirement parameters in this direction, this would improve the cost saving potential of the Spectra Optia system. However, the EAC was unclear why the company did not adopt a scenario whereby Spectra Optia has slower cessation of chelation compared to the base case or that manual RBCx also enables the cessation of chelation therapy.

The company performed a threshold analysis of chelation costs and calculated that, over the course of 5 years, Spectra Optia would always be cost saving if total chelation costs were £70,800 or less, with lower figures for the paediatric cohorts. Assuming the base case annual cost of £21,022, Spectra Optia would be cost saving if chelation could be stopped after 2.9 to 3.4 years of treatment. The company stated that advice they had received from clinical advisors indicated that in most cases chelation could be stopped before this (although the EAC could not validate this information, as the source(s) were not made explicit by the company). The EAC considered that there is no clinical evidence to accurately quantify cessation of chelation on automated RBCx, and the possibility of cessation of chelation on manual RBCx had not been considered adequately.

EAC's summary of sensitivity analysis

The company produced a large volume of sensitivity analyses to test the results from their model. Interpretation was difficult because of the adoption of the 12 subgroups. In general, the sensitivity analysis showed that the Spectra Optia system was sensitive to changes in procedural costs (in particular requirement for packed RBC) and that top up transfusion was sensitive to changes in chelation costs. Manual RBCx, which had higher procedural costs (through staff time and grade, and greater need for red blood cell units) than top up transfusion and higher chelation costs than with the Spectra Optia, was rarely the lowest cost modality. Stroke and emergency hospital admissions had little impact on the sensitivity analysis except some extreme threshold scenarios.

The EAC welcomed these sensitivity analyses which highlighted that the ordering of results was most sensitive to assumptions on the frequency of procedures, their relative costs and the assumptions on chelation cost and rate of reduction in its usage. The robustness of the base case values for these parameters is key to establishing the information content of the modelled results.

As noted in Section 4.2.5, the EAC was concerned that the underlying clinical parameters (estimates of rate of stroke, hospital admission, and requirement for chelation) were not robust. These analyses reduce the concern somewhat about including rates for stroke and hospital admissions in the model. These are materially less important than chelation costs. Thus having robust estimates of change in chelation

rates following adoption of the Spectra Optia and manual RBCx is vital. The EAC was particularly concerned that the benefit of undertaking the latter may be understated in the model.

The EAC also judged that the cost of managing iron overload were understated, being limited to medicine-related costs and not capturing the cost of MRI and other diagnostic and monitoring tests, as well as management costs arising from poorly controlled iron overload. The sensitivity analyses indicated that increasing these costs increased the likelihood that the Spectra Optia system would be the least costly modality.

However, by varying parameters around a central mean value, the analyses did not adequately address the underlying uncertainties and limitations of the evidence base used to inform the model.

These issues are discussed further in Section 4.4.

4.3.3 Exclusion of capital and maintenance costs

Company's appraisal of issue

Capital and maintenance costs were not included in the *de novo* economic model for the reasons provided in Section 4.2.6 (being that the device has multi-functionalities).

The company calculated correctly that the total capital and maintenance cost of one Spectra Optia system over the 5 years was £74,912. In the worst case scenario where a small centre treated only 5 patients with SCD, and the system was not used for other purposes, this would equate to a price of around £15,000 per patient. The company argued that even including these costs, the Spectra Optia system would still have lower total costs than manual RBCx.

The Spectra Optia would be expected to be useful beyond the life of the model. Therefore amortisation of costs over 10 years was likely to be more realistic, and the company predicted there would be additional clinical benefits for patients (reduced strokes and emergencies) over this time as well

EAC's opinion of issue

The EAC took advice from a member of the NICE Costing Team who recommended that the base case would normally include all capital and maintenance costs. When the company can identify possible alternative uses for the equipment, it would be appropriate to conduct sensitivity analyses which adjust the modelled costs by allocating some of these to other uses, using time as the apportionment basis.

The EAC has adopted this advice and undertaken additional work on this aspect (see Section 4.5). This adopted a life of 7 years for the device, consistent with information provided in confidence.

Subgroup analysis

The base case of the company's model simulated 12 subgroups of patients. As such, the company did not attempt further subgroup analysis. The EAC agreed that given the limited evidence base, further subgroup analysis would not be feasible.

Model validation

In Section 9.7.1 of the company submission, the company stated that the following methods were used to validate the model:

- The collation of values for parameters extracted from the literature was checked by a second analyst.
- Model assumptions and some parameters were commented on by clinical experts.

The EAC has been provided with a copy of the company's responses from clinical advisors and where possible has attempted to corroborate these with the model inputs used, but this was not always possible. Whilst clinical advisors provide vital information, particularly for highly technical topics where primary published evidence is scarce, their contribution to economic models, particularly regarding the quantitative inputs required for populating model parameters, should be treated with caution. In the case of the treatment of SCD using transfusions, there appears to be considerable variation in practice and the clinical experts would be constrained by this. Many experts only have direct experience in one of the treatment modalities, limiting their knowledge of the other modalities. Finally, experts are generally constrained by the questions they are asked, which can be leading. This introduces another potential element of bias on the behalf of the company.

4.4 Interpretation of economic evidence

4.4.1 Consistency with published economic literature

In Section 9.8.1 of the company submission, the company reported that there was a lack of published economic analyses identified in the literature to adequately inform or validate the *de novo* model. The company reported that the seven studies that were identified "were simplistic and poorly reported". The EAC agreed with this view. The

identified economic studies were limited to procedural costs and in general found that these were greater for automated RBCx than for the comparators. Results from the company's model supported these findings, but the inclusion of clinical outcomes, in particular the requirement for chelation, made the Spectra Optia cost saving in many of the scenarios analysed.

4.4.2 Relevance to patients and NHS settings

In Section 9.8.2 of the company submission, the company stated simply "Yes" in response to the question "Is the cost analysis relevant to all groups of patients and NHS settings in England that could potentially use the technology as identified in the scope".

The EAC agreed that the company had captured most of the relevant patients in their model; that is, patients indicated for automated or manual RBCx. Other groups of patients who may be indicated for elective RBCx but were not represented in the model included women with painful crises in pregnancy, women with fetal complications in pregnancy, pulmonary hypertension, and SCD associated leg ulcers [26]. However, the EAC appreciated that it would not be feasible to represent all affected patient groups in an economic analysis.

Regarding settings, the EAC considered that the device could be used in an alternative setting to specialist care centres. This is discussed in Section 5.

4.4.3 Strengths and weaknesses of analysis

In Section 9.8.3 of the company submission, the company provided a comprehensive list of the strengths and weaknesses of the economic submission. The EAC has addressed these in the following sections.

Strengths of the economic model

> "The model compares automated RBCx against both transfusion modalities that are in common use in the UK."

The EAC did not consider that top up transfusion was an equivalent comparator to Spectra Optia, for the reasons stated in Section 2.3.4. However, exclusion of this comparator does not directly affect the economic comparison between Spectra Optia and manual RBCx.

> "Many of the parameters used are based on values collated from several published studies, many of which are relatively recent".

The EAC had four major concerns about the company's use of values from recent studies. Firstly, many of the studies used to populate the model parameters were not published or peer-reviewed, were poorly reported, and were generally of poor methodological quality. None of the studies reported in the clinical evidence section were prospective comparative studies. Secondly, studies introduced in the economic sections were not critically appraised by the company or the EAC. Some of these studies appeared to be in populations that were not relevant to all the subgroups undergoing analysis, or featured results from mixed treatment cohorts. Thirdly, due to inadequate literature search techniques, it was not clear how some of the studies had been selected and this led to the potential for 'cherry picking' of studies. Finally, it was not clear to the EAC how results had been collated, if weighting had been applied, and on occasions specific values were opaque. Distributional data was not provided for any of the clinical parameters.

> "The model accounts for multiple subgroups within the transfused sickle cell patient population. Adults and children are often treated at different centres so that separating the analysis allows the outcomes to be relevant to more services. It allows differences in the cost-savings between patient groups to be described".

The EAC considered that this was true; however, as medical technologies guidance are intended to be used as national guidance, a single estimate of the cost saving potential would have been useful.

> "The published data that we have used appears to be relatively conservative when compared to information from NHS hospital websites, leaflets and procedures. One clinical adviser indicated that the rate at which patients without pre-existing overload would require chelation therapy was under-estimated in our model. This would have the effect of under-estimating savings from using automated RBCx. The cost-savings we have identified should therefore be comfortably realisable in practice."

The EAC considered that published data (where possible peer-reviewed) should take precedence over the other information sources cited and expert opinion, so should not be regarded as conservative in this regard.

> "The model takes into account several important clinical outcomes (stroke, hospital admissions, need for chelation therapy) that have not previously been identified as costs."

The EAC considered that although this was true and these are clearly important costs in the management of SCD, it was not possible to reliably quantify the rate of these clinical

outcomes using the available data. Some of these outcomes were not reported in the clinical evidence sections of the submission.

> "The overall costs primarily comprise RBC usage and chelation medication. There is some uncertainty regarding the absolute proportions of patients taking chelation, the dose they are taking and the timepoint at which they start and stop. However, these resources are relatively easy to quantify for potential adopters to calculated their own values."

The EAC considered that although resource use of chelation and blood use is relatively easy to quantify, as the company alluded to, the comparative rates of iron overload between modalities is not. This gap in the knowledge base will not help potential adopters.

> "The model time horizon of 5 years is long enough to represent appropriate outcomes and changes in iron status of patients, but also short enough for cost-savings to be relevant to commissioners. Cost-savings would be expected to increase as the time-horizon is extended."

The EAC agreed that 5-years was an appropriate time perspective for the model, for the reasons suggested.

> "Extensive deterministic sensitivity analysis demonstrates that automated RBCx remains cost-saving with respect to manual RBCx in the vast majority of realistic circumstances."

The EAC judged that the deterministic analysis was informative in identifying the key drivers of the model but it did not adequately address the underlying uncertainties and limitations of the model.

Weaknesses of the economic model

> "Adverse events are not included. Common events were considered to be mild and have negligible associated costs. More severe events were rare and although incurred considerable costs for acute treatment were not considered to differ between transfusion modalities".

The EAC acknowledged this was a weakness of the model; however, with the available data it would not be possible to rectify it.

> "There are significant uncertainties in the rates at which patients will become iron overloaded when receiving manual RBCx, and at which iron levels return to

normal when receiving automated RBCx and chelation therapy. However, using rates in the base case that would tend to favour the comparators still demonstrated substantial cost savings for automated RBCx in many patient subgroups."

The EAC considered that it was not possible to know if the base rate assumptions about chelation favoured the comparators or not. In particular, for manual RBCx, it was assumed that nobody with existing iron overload could cease chelation, despite manual RBCx being an 'iron neutral' treatment, in principle. Similarly in the model, 50% of patients without initial iron overload required chelation after two years whilst on manual RBCx. This did not seem to be informed by published evidence or expert advice.

"We received additional information regarding rates of chelation cessation from two clinical advisers that was received too late to incorporate fully into the base case and sensitivity analysis. Although this has been tested using scenario and threshold analysis we would have preferred to model these values fully".

"Due to the timescale for the work it was difficult to obtain sufficient relevant input from clinical advisers. By requesting clinical input early the information provided was not fully relevant to the final model, and requesting additional information later produced a low response rate."

The EAC considered these were not weaknesses of the model per se but on the process of acquiring data to populate the model with. The EAC agreed that this was a weakness.

"Probabilistic sensitivity analysis was not conducted, partly due to time constraints. However, the number of SCD patients receiving regular transfusion therapy in the UK is around 500-600, with no more than around 60 patients treated at any one centre. Therefore, the subgroup analyses and deterministic sensitivity we have conducted should provide sufficient information for potential adopters".

The EAC did not understand the relevance of the population or centre size to the application of probabilistic sensitivity analysis. The main barrier to performing sensitivity analysis appeared to be the lack of relevant distributional data available.

Summary of strengths and weaknesses of model

The EAC has summarised what it considers to be the related strengths and weaknesses of the model in Table 4.3.

Table 4.3. *Relative strengths and weaknesses of the company's de novo model.*

Strengths of model	Weaknesses of model
Relevant to scope in terms of population, intervention, comparators, and some outcomes.	Included top up transfusion which was not specified in scope.
Bases case analysis consisted of 12 subgroups, representing heterogeneous nature of SCD population.	Proportion of these subgroups in population not known, so not possible to calculate a single figure for cost saving.
Included important clinical outcomes such as stroke and acute crises (using surrogate measure of hospital readmission).	Large uncertainty in event rates of clinical outcomes due to inadequate clinical data, particularly regarding incremental benefits of automated RBCx.
Included chelation costs which are widely known to be a major cost factor in the treatment of severe SCD.	Not possible to quantify requirement for chelation from clinical evidence base. "Best guess" approach used likely to be subject to bias. Other costs associated with iron overload not in model (e.g. monitoring and treatment costs). This would lead to an underestimate of cost saving potential for Spectra Optia (if iron overload data is accurate).
Extensive analysis on resource uses, particularly procedural costs.	Cost of clinical outcomes difficult to estimate.
Extensive deterministic sensitivity analysis.	Did not address the most important elements of uncertainty in the model.
	Did not include capital, training, or maintenance costs of Specta Optia system. Discussed in Section 4.3.3.

4.4.4 Further analyses

In Section 9.8.4 of the company submission, the company recognised that a major limitation of the model was the uncertainty surrounding the requirement for chelation, the number of procedures per year and the number of red blood cell units used per procedure. The company suggested that a solution to this would be to acquire further data through local audits. The EAC considered this was a useful suggestion, could be achievable, and would add value to the present or future model. The EAC has discussed future research options in Section 6.

4.5 Additional work undertaken by the External Assessment Centre in relation to economic evidence

As described in previous sections, there were a paucity of quality data available to populate the company's model and as such the EAC has adjusted some of the company's assumptions to assess their impact upon the results of the model. Those assumptions and input parameters changed by the EAC within their modelling scenario are described in Section 4.5.1. All other inputs remain the same as those used within the company's analyses. Many of the assumptions retained from the company's modelling were based on weak evidence. However, the EAC agreed that based on the EAC's clinical expert opinion and evidence base available the assumptions were reasonable, although lacked certainty.

Section 4.5.1 sets out the inputs used by the EAC. Given the lack of data available and the uncertainty around the values that are published, these inputs represent the values the EAC's judges are representative of the evidence. However, the data limitations and hence poor confidence in the results remains the key issue when interpreting them.

4.5.1 EAC's model input parameters

Cost of Spectra Optia

Within the company's base case, the capital and maintenance costs of the Spectra Optia device were not included. The EAC has updated the analysis to include the cost of both purchasing and maintaining the device. These costs, shown in Table 4.4, were obtained from the company submission and spread over the 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 28 patients and 18 patients per year (information provided in confidence). These numbers

have been rounded to investigate a slightly larger range, such that the results of the EAC's analyses are reported for both 15 and 30 patients using the device 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.

Table 4.4. *Cost of Spectra Optia device*

Parameter	Input value	Source
Cost of purchasing a Spectra Optia device	£52,052	Company submission (cost of device and software)
Cost of Spectra Optia maintenance per year	£4,572	Company submission (service charge)
Lifespan of device (years)	7 years	Information provided in confidence
Number of patients using device per year	15-30 patients	Rounded from information provided in confidence

Within the company submission, the capital cost of the Spectra Optia device was not included because the device can be used for multiple functions, benefitting patients outside the scope of this assessment. The EAC has included within its adaptation of the model the functionality to attribute some of the costs of the device to patients outside the scope of this assessment. To be conservative, 100% of the device usage and costs are attributed to patients within the scope in the base case. However, it is estimated that based on 30 patients per year having an average of 8.5 automated blood exchanges per year, each taking around 2 hours, the device will be required for these purposes 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. Hence, around 70% of Spectra Optia will be spare capacity. In reality, this figure will likely be reduced as there is the need to move equipment and block sessions. As such, it is estimated that based on 30 patients undergoing automated exchange, 50% of the capacity of Spectra Optia will be utilised. A similar calculation was undertaken and conservatively rounded to determine that where 15 patients undergo automated transfusion each year with a device, 70% of its capacity can be used elsewhere. This will be considered when looking at the certainty around the results of the EAC's modelling scenario.

Cost to manage iron overload

Currently the company submission only includes medication costs but hospitals will also incur diagnostic and monitoring costs. In addition, there are potential costs from managing patients with poorly controlled iron management who develop disorders, primarily in the liver, but not limited to that organ. Insufficient time has precluded costing these fully. The EAC does, however, have information provided in confidence which identifies the savings from drugs and diagnostic tests. These show savings in the ratio 1:0.64 between drugs and diagnostics. The EAC has increased the chelation drug costs by this ratio to approximate these wider management costs. The impact is shown in Table 4.5

Table 4.5. *Cost of chelation therapy per patient adopted by EAC and company*

	EAC	Company	% Increase
Adults	£34,520	£21,022	64
Children	£16,345	£9,954	64

The chelation costs derived by the company were based on all patients being treated with the oral chelation medication, deferasirox (Exjade). This medication appears to be the preferred treatment for patients with iron overload [60]. However, the National Haemoglobinopathy Registry Report indicates that whilst approximately 70% of patients are treated with the oral chelation medication, the majority of the remaining 30% are treated with a cheaper intravenous drug, desferrioxamine [34]. The EAC undertook targeted literature searching to identify cost data for both drugs. In 2006, The Scottish Medicine Consortium advised the annual cost for adults of deferasirox ranged from £15,288 to £30,576 and for desferrioxamine from £3,464 to £16,169 depending on patient body weight [77]. These are drug costs only and do not factor in different administration, monitoring and adverse event profiles.

In 2008, the All Wales Medicines Strategy Group addressed these wider factors [78]. Its analysis concluded that in patients with SCD, deferasirox had £930 lower annual costs than desferrioxamine. There is no guidance from NICE on these drugs.

The EAC has decided to retain the company's estimated medication costs for chelation, noting that although desferrioxamine is used, its total costs may exceed those with deferasirox.

Chelation therapy: TUT without iron overload

The company had assumed a proportion of 90% of patients undergoing chelation therapy as a consequence of prior TUT in years 2 to 5 of the model. These patients entered the model with no iron overload. The EAC has updated this value to 75% based on 250 of 332 patients in the Haemoglobinopathy Registry Report receiving regular chelation therapy [34].

Units of RBC used during manual exchange

Within the company submission the number of RBC units used during manual blood cell exchange was assumed to be equal for adults and children (4 units each). The EAC judged that it is unlikely that children will require the same number of RBC units as adults and therefore updated this assumption such that 3 RBC units are required for children.

Duration of manual exchange procedure

Due to the EAC's update of the assumption for the number of RBC units required for children undergoing manual exchange, the EAC judged the procedure time should be updated, likewise. Although the number of RBC units required for children were deemed to be 75% of those required for adults, this proportion was not applied to procedure time due to issues of venous access, pressures and flow rates. Therefore, a more valid assumption was judged to be that the duration of the procedure for manual exchange should be 85% of the time for adults. This assumption was based on the comparative exchange duration time provided by Quirolo *et al*. (2015) [11]. As a result, the duration of manual exchange in children was updated from 245 minutes to 208 minutes.

Number of staff per patient

The company's model assumed that 1.5 staff members per patient were present during manual exchange. Based on expert opinion (see EAC Correspondence Log), the EAC judged that only 1 staff member per patient is likely to be required for manual exchange. There was variation within the EAC's clinical expert opinion, with one expert suggesting multiple patients could be supervised by one staff member during automated exchange (see EAC Correspondence Log). To be conservative, the EAC has assumed that one staff member per patient is required for both manual and automated exchange. However, this may underestimate the benefits of automated exchange.

Table 4.6 provides a summary of the model inputs that have been updated by the EAC.

Table 4.6. *Summary of model inputs updated by the EAC*

Input parameter	Value
Capital cost of Spectra Optia (over model time horizon per patient). Range refers to 30 or 15 patients using 100% of the device's capacity per year. The values in brackets are those costs without full capacity.	£1,178- £2,356 (£589-£707)
Maintenance cost of Spectra Optia (over model time horizon per patient). Range refers to 30 or 15 patients using 100% of the device's capacity per year. The values in brackets are those costs without full capacity.	£712-£1,424 (£356-£427)
Use of device capacity. Range refers to capacity used with 15 and 30 patients per year.	30% - 50%
Cost to manage iron overload	Adults £34,520 Children £16,345
Chelation therapy: TUT without iron overload	75% in years 2-5
Units of RBC used during manual exchange: children	3 units per procedure
Duration of manual exchange: children	208 minutes
Number of staff per patient: manual exchange	1 staff member per patient

4.5.2 Results of EAC's analysis

The results of the company's model using the EAC's assumptions and inputs are presented in Table 4.7. The main results in this table are based upon 30 patients using Spectra Optia for automated exchange per year with the full costs of the device being incurred by these patients. The results provided in brackets are again based on 30

patients using the device for automated exchange each year, with 50% of the device costs being incurred by patients within the scope of this assessment and the reminder by other patients.

Table 4.7. *Results of EAC's cost analysis (30 patients per year)*

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 primary prevention	Optia	£51,450 (£42,994)	£73,267 (£64,811)	£107,188 (£98,731)	£113,820 (£105,364)
	Manual	£44,542	£92,577	£92,577	£92,577
	TUT	£66,218	£89,934	£89,934	£89,934

In Table 4.8 and Table 4.9 the incremental results of the cost analysis are presented based on both 30 patients using Spectra Optia for their automated transfusion each year at both 100% and 50% use of the device's capacity. A negative incremental cost indicates that automated exchange is cost saving over the alternative.

Table 4.8. *Incremental results of EAC's cost analysis (30 patients per year, 100% of device capacity)*

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

Table 4.9. *Incremental results of EAC's cost analysis (30 patients per year, 50% of device capacity)*

Population	Option	No overload	Mild overload	Moderate overload	Severe overload
Adults	Auto-manual	-£16,555	-£71,925	-£287	£13,721
	Auto-TUT	-£69,027	-£73,037	-£1,399	£12,609
Paediatric secondary prevention	Auto-manual	-£3,983	-£30,200	£3,720	£10,353
	Auto-TUT	-£26,967	-£28,866	£5,054	£11,687
Paediatric primary prevention	Auto-manual	-£1,548	-£27,766	£6,154	£12,787
	Auto-TUT	-£23,224	-£25,123	£8,797	£15,430

Table 4.10 presents the results based upon 15 patients using Spectra Optia for automated exchange per year with the full costs of the device being incurred by these patients. The results provided in brackets are again based on 15 patients using the device for automated exchange each year, with 30% of the device costs being incurred by patients in the scope of this assessment and the reminder by other patients.

Table 4.10. *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

In Table 4.11 and Table 4.12 the incremental results of the cost analysis are presented based on 15 patients using the Spectra Optia device for their automated transfusion each year. A negative incremental costs indicates that Spectra Optia is cost saving over the alternative.

Table 4.11. *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-manual	£8,814	-£46,556	£25,083	£39,090
	Auto-TUT	-£43,658	-£47,668	£23,970	£37,978
Paediatric secondary prevention	Auto-manual	£21,386	-£4,831	£29,089	£35,722
	Auto-TUT	-£1,598	-£3,497	£30,424	£37,056
Paediatric primary prevention	Auto-manual	£23,821	-£2,397	£31,524	£38,156
	Auto-TUT	£2,145	£246	£34,166	£40,799

Table 4.12. *Incremental results of EAC's cost analysis (15 patients per year, 30% of device capacity)*

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

The final table, Table 4.13, provides an overall summary of the results of the four scenarios considered by the EAC, broken down by patient subgroup.

Table 4.13. *Summary of scenarios considered by EAC*

Population	Option	No overload	Mild overload	Moderate overload	Severe overload
Adults	Auto versus manual	Generally, Spectra Optia is cost-saving, except where extreme assumptions are used	Spectra Optia is comfortably cost saving over manual	Spectra Optia is cost-saving over manual where the less conservative assumptions are used	Spectra Optia is always more costly than manual
	Auto versus TUT	Spectra Optia is comfortably cost saving over TUT	Spectra Optia is comfortably cost saving over TUT	Spectra Optia is cost-saving over manual where the less conservative assumptions are used	Spectra Optia is always more costly than manual
Paediatric secondary prevention	Auto versus manual	Spectra Optia is cost-saving over manual where the less conservative assumptions are used	Spectra Optia is comfortably cost saving over manual	Spectra Optia is always more costly than manual	Spectra Optia is always more costly than manual
	Auto versus TUT	Spectra Optia is comfortably cost saving over TUT	Spectra Optia is comfortably cost saving over manual	Spectra Optia is always more costly than manual	Spectra Optia is always more costly than manual
Paediatric primary prevention	Auto versus manual	Spectra Optia is cost-saving over manual where the less conservative assumptions are used	Spectra Optia is comfortably cost saving over manual	Spectra Optia is always more costly than manual	Spectra Optia is always more costly than manual
	Auto versus TUT	Generally, Spectra Optia is cost-saving, except where extreme assumptions are used	Generally, Spectra Optia is cost-saving, except where extreme assumptions are used	Spectra Optia is always more costly than manual	Spectra Optia is always more costly than manual

From Table 4.13, it is apparent that Spectra Optia is potentially cost-saving in patients with no or mild iron overload, but is potentially cost-incurring in those patients with moderate or severe iron overload. In patients with greater iron overload there is assumed to be a smaller reduction in the proportion of patients requiring chelation therapy. The assumed rate of relative change in chelation rates, by grade of iron overloading, with each modality is very poorly evidenced. As noted in Section 4.2.2, the adoption of 12 subgroups requires assumptions to be made based on outcomes which are not reported to this level of disaggregation. A related limitation of the model structure and the data available to populate the model, given that the proportion of patients on chelation therapy is split by degree of iron overload for Spectra Optia, but not for manual exchange or top-up transfusions. This means that it is likely that in the model the proportion of patients requiring treatment for overload having had manual exchange is overstated for the milder overload subgroups and understated for the more severe overload subgroups.

Therefore, the EAC strongly advises that these results for individual subgroups should not be used to judge the relative cost-effectiveness in each of the four iron overload categories. Generally, the results of the model should be interpreted with caution given the paucity of good quality data available to populate the model.

The EAC has not identified any information source via targeted literature searches providing the percentage of the SCD population within each subgroup, or even by severity of iron overload. Hence no weighted total cost for each comparator can be calculated.

4.5.3 NHS Blood and Transplant Therapeutic Apheresis Services (TAS)

It was initially suggested by the company at the introductory teleconference with the EAC that local NHS trusts can potentially buy Spectra Optia automated RBCx sessions from one of 6 regional NHS Blood and Transplant Therapeutic Apheresis Services (TAS) [27] (see EAC Correspondence Log). However, this service delivery model was not subsequently described in the company submission of economic evidence. The EAC therefore sought to independently confirm this route to access automated RBCx, given the special consideration described by NICE in the statement of the decision problem that: “There is currently an inequity of access to the highest standards of care for sickle cell disease as treatments are only available in certain cities in the UK.” [14].

TAS services are delivered across England and North Wales from six therapeutic apheresis units, five of which offer RBCx (Bristol, Oxford, Leeds, Sheffield and Liverpool TAS Units). Thirty NHS trusts have referral pathways

through local service level agreements with TAS and patients can be referred for automated RBCx using a standard form. The EAC emailed an information request to the NHS Blood and Transplant Service on 27/07/2015, seeking additional details, with costs. A comprehensive response was received on 03/08/2015, with request for information on pricing to be redacted from the public documents (see EAC Correspondence Log).

In summary, the NHS Blood and Transplant Service recognise that they currently undertake a low level of RBCx activity across the service when compared to potential demand. Last year the TAS delivered around 170 RBCx procedures. Treatment prices are agreed with the Department of Health national Commissioning Group as part of an annual price setting process. Their existing pricing is based on a full cost recovery methodology which includes direct, indirect and unallocated overhead costs. Treatments are charged to Trusts on a cost per procedure basis. The procedure price includes review and acceptance of the referral by a TAS Consultant Haematologist and for a member of the team to undertake the actual automated exchange (TAS provides the equipment and consumables). The price excludes the price of replacement fluids i.e red cells. A red cell exchange undertaken in one of the five TAS Units is [redacted]. Different premiums apply if the procedure is undertaken in a different part of the hospital, at another hospital and/or out of hours. The maximum charge for a procedure undertaken in another hospital outside of normal working hours is [redacted].

4.5.4 Estimated size of patient population for automated RBCx in SCD

It has been estimated that there are around 13,500 people in England with sickle cell disease, affecting over 1 in 2000 live births [79]. The NHS Sickle Cell and Thalassaemia Screening Programme also anticipates that the birth prevalence in some urban areas may be as high as 1 in 300. In an NHS Trust in London, it has been estimated that 10-20% of patients with SCD require regular blood transfusions or red blood cell exchange (information provided in confidence), although this figure may be slightly higher than the national average, due to the higher prevalence of SCD in London.

The National Haemoglobinopathy Registry (NHR) Report (2014) has identified that, as of March 2014, a total of 7338 patients from 49 centres were registered within the Registry. In the live registry, this figure had reached 9642 patients from 52 centres by mid-July 2015. It is anticipated that this figure is not an accurate representation of the current prevalence of sickle cell disease. This is due to the possibility of patients who have not provided consent for data entry to the NHR. Also, as patients may be enrolled at different centres, there is the potential for double counting within the registry.

From the NHR, it is clear that the prevalence of sickle-cell disease varies considerable across different regions of the country, with a particularly high density of patients with the disease in London, Birmingham and the North West. Specifically, the registry reports 4558 patients with sickle cell disease residing in London and approximately 400-500 in areas such as the North West, Yorkshire and Humber and the West Midlands.

From the data presented in the NHR Report, it is evident that of the 7338 patients who are registered within the registry, approximately 600 are receiving a form of transfusion and approximately 250 are receiving chelation therapy. The transfusion data revealed that 55% (332/606) patients receiving transfusion are on a regular transfusion regime. It is therefore calculated that 4.5% of patients with sickle cell disease in the Registry are receiving a chronic transfusion regime, although the method of transfusion and proportions of automated to manual RBCx are not currently reported. It is also noted that approximately 5% (20/400) of patients in Birmigham require a chronic RBCx transfusion regime (information provided in confidence). The differences between London and the national figures is likely to reflect the varying prevalence of SCD across the different regions.

Data in the registry also identify the geographical location of patients referred to London for treatment. This demonstrates that patients from as far as the Scottish borders, the South West and North Wales are receiving transfusion therapy SCD in London.

The EAC therefore concludes that the upper limit of unmet need for automated RBCx is 5 to 10% of all patients with SCD.

4.6 Conclusions on the economic evidence

The company developed a basic economic model that aimed to estimate the overall procedural and clinical costs associated with 5 years management of chronic, severe SCD using automated RBCx (the Spectra Optia system), manual RBCx, and ‘top up’ transfusions. The EAC cautioned that top up transfusion was not in scope and hence not a valid comparator. Due to the heterogeneous nature of the population being simulated, 12 subgroups with different baseline characteristics and chelation requirements were modelled. This meant that an overall ‘average’ cost of management per person with SCD could not be calculated, nor the overall budgetary impact of adoption of Spectra Optia.

The company reported that, in the base cases, Spectra Optia was always cost saving compared to manual RBCx, with savings ranging from £360 to £52,516. In half of the scenarios (6/12), top up transfusion was cost saving compared with automated RBCx. The costs driving these results were the

different procedure related costs and frequencies and the benefits from reduced iron overload. For top up transfusions, chelation costs were the most significant parameter in informing the ordering of results. Manual RBCx was associated with relatively high procedural and chelation costs, which accounted for its increased costs compared with the other modalities.

The company conducted extensive univariate, threshold and sensitivity analysis for each subgroup presented in the model. These were mainly based on adjusting healthcare resources and unit costs, and in general favoured Spectra Optia. The EAC considered the sensitivity analyses were of limited value, because they did not challenge the underlying structure of the model or address its limitations.

The EAC considered that the model had several shortcomings. In their justification for the model structure (Section 9.1.5); the company stated that they "had chosen not to represent these as health states as we have no data on which to base transition probabilities". The EAC agreed that data was lacking to inform a full decision analytic model. However, despite this, the company included clinical outcomes in the model including secondary stroke, complications of SCD requiring hospital admission, and requirement for chelation. Event rates were calculated as crude annual or five year rates. The EAC considered that the data used to inform these rates were subject to a high degree of bias and uncertainty such that these elements of the model were effectively unproven.

In particular, the EAC was concerned that the estimates for different event rates between automated and manual RBCx were not substantiated by robust evidence. Concerns included in respect of hospital readmissions where the evidence appeared to be highly selected, and for stroke, where the value for manual RBCx appeared to unsupported by evidence and compared against an implausible rate of zero for automated RBCx. The EAC considered that the assumption that the requirement for chelation may be reduced was consistent with the (poor quality) clinical evidence presented and with expert opinion; however, the specific values for the requirement for chelation, particularly in the manual RBCx arm where no data was supplied, were also unsubstantiated and represented little more than a 'best guess' estimate. In addition, the EAC did not consider the sensitivity analyses adequately addressed the uncertainty surrounding these assumptions and estimates.

The EAC reviewed the cost inputs into the model and agreed most were reasonable and were tested adequately with sensitivity analysis. The exception is the cost of chelation which was limited to the medication related costs only. However, the cost estimates are of secondary importance if the underlying clinical assumptions and estimates are not valid or verifiable.

Implementation of the Spectra Optia system requires a significant financial outlay, and this cost, along with ongoing maintenance, was excluded in the model.

The EAC has addressed some of these omissions in its additional work (Section 4.5.2), by performing additional analysis using the company's model. The EAC's analysis included the capital and maintenance costs of the Spectra Optia system, as well as revised estimates for the cost of chelation, and adjusted procedural costs concerning staffing and red blood cell usage (in children). Using these revisions, the EAC found that the Spectra Optia was potentially cost saving in patients with no or mild iron overload, but potentially cost incurring in patients who have moderate or severe overload (Table 4.13). It should be emphasised that these results are subject to the same uncertainty as those of the company, and the clinical requirement for chelation in particular remains an area of uncertainty. However, if the underlying assumptions of the model are considered to be plausible, and if this is reflected in real-life improvements in prevention of iron overload, then the revised model adds confidence in the cost saving potential of the Spectra Optia system.

In summary, the EAC considered the clinical benefits of exchange transfusions where indicated for the chronic management of severe SCD are not in doubt, with evidence showing that appropriate management using this treatment can reduce the likelihood of serious complications of SCD occurring (including stroke, painful crises and acute chest syndrome) [25, 26, 32, 80]. However, the specific issue for the development of this medical technologies guidance is whether the incremental change from manual RBCx to automated RBCx using the Spectra Optia system would be cost neutral or cost saving. In the opinion of the EAC, this has not been adequately proved by the company's model. The EAC considered that:

- The main flaw of the model was that it relied on clinical assumptions and rate estimates that could not be substantiated by the available clinical evidence. This consequently led to unacceptable uncertainty and a lack of confidence in the results generated.

- Longer term cost savings through clinical superiority, particularly through reduced requirement of chelation, were plausible, but could not be quantified using the available clinical data. Over time these could balance or outweigh the increase in procedural costs associated with the Spectra Optia system, but this is unproven at present. This uncertainty cannot be resolved entirely using the present or similar models without additional data on the incremental differences between manual and automatic RBCx being made available. If it is unlikely that

these data will be forthcoming in the future (see Section 6) then more reliance may need to be placed on the judgment of clinical experts, drawing on their knowledge of the outcomes from the different modalities. Obtaining such views may be easier if some subgroups are consolidated.

The Spectra Optia system may have other tangible advantages compared with manual RBCx which have not been quantifiable in the model submitted or in the EAC's modifications to it. These include:

- Reduced procedure times and intervals between procedures. Although the released costs associated with these were included in the economic model, the benefits these add to the patient experience and potential improved compliance were not.
- Reduced variability in clinical practice, helping to standardise the treatment of patients with SCD on a local and national level.
- Improved safety and auditing of exchange procedures.
- In some patients, use of depletion-exchange to optimise treatment, with the possibility of reduced RBC consumption.
- Use in other indications such as plasma exchange apheresis.

The EAC considers if all of these advantages were to be considered holistically it is plausible that the Spectra Optia system offers a 'better way of doing things' compared with the non-standardised practice of manual RBCx. Collectively, these advantages might ultimately involve system benefits which are resource saving. Additionally, the EAC believes there may be scope to include the Spectra Optia system as part of an improvement in commissioning of services to people with SCD. This is discussed in Section 5.

Impact on the cost difference between the technology and comparator of additional clinical and economic analyses undertaken by the External Assessment Centre

Table 4.14 and Table 4.15 display the impact of each of the EAC's changes on the results of the model. For clarity, these are shown for two subgroups and show the incremental results for Spectra Optia versus manual exchange only. The subgroups selected were adults with mild iron overload and paediatric secondary prevention with severe iron overload. These were selected to represent subgroups in which Spectra Optia is both cost saving and cost incurring. Further, the results are presented based on 30 patients using the device for exchange each year, with no spare capacity attributed to patients outside the scope of this evaluation.

In patients with mild overload, the EAC's increase in chelation costs outweighed the cost incurred by including capital and maintenance costs of Spectra Optia. The difference in the proportion of patients requiring iron overload therapy in this subgroup was a key driver in the estimated cost-saving generated.

In patients with severe overload, a higher proportion of Spectra Optia patients have iron overload therapy than manual and TUT patients and therefore the increase in cost of this therapy combined with the inclusion of capital and maintenance costs results in Spectra Optia becoming cost incurring compared with manual exchange.

Table 4.14: *Impact of parameter changes to the de novo model: Adults with mild iron overload – Spectra Optia versus manual exchange*

Action	**Incremental cost per patient**	**Change from sponsor's base case**	**Percentage of base case incremental cost**	**Impact of action (compared with the sponsor's deterministic base case incremental cost of -£52,517 per patient)**
Inclusion of capital costs of device	-£41,657	£10,860	79%	The inclusion of capital costs reduces the incremental cost savings with Spectra Optia as the Spectra Optia arm is now more costly.
Inclusion of maintenance costs of device	-£46,463	£6,054	88%	The inclusion of maintenance costs reduces the incremental cost savings with Spectra Optia as the Spectra Optia arm is now more costly.
Iron overload treatment costs per year: Adults	-£84,961	-£52,517	162%	Including diagnostic and monitoring costs to increase the cost of iron overload treatment increases the cost-savings with Spectra Optia. This occurs as a greater proportion of manual exchange patients require this expensive treatment.
Chelation therapy: TUT without iron overload	N/A	N/A	N/A	This change is not applicable to this subgroup. In patients with no iron overload, TUT becomes less costly given that fewer patients require chelation. Hence, the cost savings with Spectra Optia reduce.
Units of RBC used during manual exchange: children	N/A	N/A	N/A	This change applies to children only (see Table 4.15).

Action	Incremental cost per patient	Change from sponsor's base case	Percentage of base case incremental cost	Impact of action (compared with the sponsor's deterministic base case incremental cost of -£52,517 per patient)
Number of staff per patient: manual exchange	-£47,937	£4,580	91%	Reducing the number of staff per patient required for manual exchange reduces the incremental cost savings with Spectra Optia due to the now lower cost of manual exchange.
All above changes made simultaneously	-£63,468	-£10,951	121%	Making all of the changes from the sponsor's base case to the EAC's base case simultaneously results in an increase in the cost savings with Spectra Optia, maintaining the direction of the results.

Table 4.15: *Impact of parameter changes to the de novo model: Children (secondary prevention) with severe iron overload – Spectra Optia versus manual exchange*

Action	Incremental cost per patient	Change from sponsor's base case	Percentage of base case incremental cost	Impact of action (compared with the sponsor's deterministic base case incremental cost of -£11,290 per patient)
Inclusion of capital costs of device	-£431	£10,859	4%	The inclusion of capital costs increases the cost of Spectra Optia, such that it is now cost incurring.
Inclusion of maintenance costs of device	-£5,237	£6,053	46%	The inclusion of maintenance costs reduces the incremental cost savings with Spectra Optia as the Spectra Optia arm is now more costly.
Iron overload	-£10,796	-£494	96%	Including diagnostic and monitoring costs to increase the cost of iron overload treatment increases reduces the cost

Action	Incremental cost per patient	Change from sponsor's base case	Percentage of base case incremental cost	Impact of action (compared with the sponsor's deterministic base case incremental cost of -£11,290 per patient)
treatment costs per year: Children				savings with Spectra Optia. This occurs as a greater proportion of Spectra Optia patients require this expensive treatment.
Chelation therapy: TUT without iron overload	N/A	N/A	N/A	This change is not applicable to this subgroup. In patients with no iron overload, TUT becomes less costly given that fewer patients require chelation. Hence, the cost savings with Spectra Optia reduce.
Units of RBC used during manual exchange: children	-£4,561	£6,729	40%	Reducing the units of RBC required for children during manual exchange reduces the cost of this treatment option. Therefore the incremental cost savings with Spectra Optia are reduced.
Duration of manual exchange: children	-£9,216	£2,074	82%	Reducing the duration of manual exchange in children reduces the cost of this treatment option. Therefore the incremental cost savings with Spectra Optia are reduced.
Number of staff per patient: manual exchange	-£6,711	£4,579	59%	Reducing the number of staff per patient required for manual exchange reduces the incremental cost savings with Spectra Optia due to the now lower cost of manual exchange.
All above changes made simultaneously	£18,809	£30,099	-167%	Making all of the changes from the sponsor's base case to the EAC's base case simultaneously changes the direction of the results, meaning Spectra Optia is no longer cost

Action	Incremental cost per patient	Change from sponsor's base case	Percentage of base case incremental cost	Impact of action (compared with the sponsor's deterministic base case incremental cost of -£11,290 per patient)
				saving compared with manual exchange.

5 Conclusions

The Spectra Optia system is an automated apheresis device that can be used for RBCx in the management of chronic SCD. It has two principal benefits. Firstly, the transfusion of donor blood improves the oxygen carrying capacity of blood and treats anaemia that occurs with SCD. Secondly, the isovolaemic removal of sickled cells reduces the risk of a vaso-occlusive event occurring, such as painful crises, acute chest syndrome, or stroke. RBCx is indicated in patients with SCD who cannot receive treatment with the fetal haemoglobin stimulating drug hydroxycarbamide, or who are refractory to this treatment. It is also indicated for the primary and secondary prevention of stroke in children considered to be at high risk [25, 26]. In general, the aim of exchange treatment is to maintain HbS levels at 30% or less [26]. Automated RBCx is regarded as 'iron neutral', meaning that iron levels in the blood are maintained at normal levels.

An alternative treatment to automated RBCx is manual RBCx. In theory, manual RBCx performs the same function as automated RBCx, and should also be considered iron neutral. However, in reality this is operationally difficult to perform, and there are variations in treatment practices and the formulae adopted to establish the appropriate volumes to transfuse. Partial exchange is also adopted for some patients which would increase iron levels [26].

Simple or 'top up' infusions may also be used. Whilst this treatment will manage anaemia, it can increase the viscosity of blood and increase the risk of vaso-occlusive events, and it is difficult to maintain HbS levels at 30% using top up transfusions alone [26]. Additionally, regular use of elective top up transfusions inevitably leads to iron overload (usually after about 20 procedures) and the requirement for chelation. Chelation therapy is often unpleasant for the patient, poorly adhered to, and expensive for the NHS. For these reasons, regular use of top up transfusions may be regarded as a suboptimal option, and in the opinion of the EAC, is not a valid comparator for automatic RBCx.

The decision problem specified in the scope was whether the use of automated RBCx using the Spectra Optia provides incremental benefits to the patient (clinical outcomes) and healthcare system (economic outcomes) compared with manual RBCx. The decision problem was *not* intended to compare RBCx with top transfusions, as the superiority of RBCx (by any means) could be considered to be self-evident [25, 26].

In the clinical evidence section of the submission, the company presented six studies that compared Spectra Optia (or its earlier variant, Cobe Spectra) with

manual RBCx [2-7]. These were retrospective observational studies, not prospective experimental trials; the quality of reporting was generally poor and only two of the studies were peer reviewed [2, 4]. In addition, the company presented 14 single armed studies of the automated systems, of which six were reported as full, peer-reviewed papers and considered further by the EAC [8-13]. As these were non-comparative studies, they offered absolute or 'before and after' results only. The EAC found that:

- There was unequivocal evidence from the reported clinical studies that Spectra Optia significantly reduced the procedure duration, increased the intervals between procedures, and increased the volume of packed RBC required.

- There was equivocal evidence that the Spectra Optia system is equivalent to manual RBCx in achieving HbS (%) and haematocrit targets. There was some evidence to suggest a trend in reduction of serum ferritin levels using automated RBCx compared with manual RBCx. However, due to the design and quality of the comparative studies that reported this outcome, the EAC considered there was considerable doubt over this, and it was not possible to extrapolate these data to calculate possible reductions in chelation requirement. The EAC also considered the evidence on reduced hospital admissions was equivocal.

- There was no published evidence presented on staff resource use; ease of venous access; quality of life; or BMI and growth in children.

- Notably, there was considerable uncertainty about the generalisability and validity of the evidence presented on clinical outcomes such as stroke, painful crises, acute chest syndrome, or other complications of SCD.

In view of the evidence gaps, the EAC invited eight clinical experts to give their opinion on the Spectra Optia system; six experts, with varying experience of manual and automated RBCx in children and in adults, responded. The experts were relatively consistent in their responses and all were generally positive about the potential benefits of the Spectra Optia system. Compared with manual RBC, the main advantages of the system appeared to be greater efficiency, increased success in achieving clinical targets (HbS, haemoglobin, and haematocrit), and reduced staffing requirements. The experts that responded were unanimous that the improved efficiency of Spectra Optia, as well as procedural difficulties associated with manual RBCx, would lead to a tendency for reduced ferritin levels for the automated technology.

To support the economic case for adoption, the company provided a *de novo* model that compared automated RBCx (Spectra Optia) with manual RBCx and top up transfusions over a 5 year time perspective. This was a simple costing model with no clinical states, but did contain costs for clinical outcomes. Costing inputs consisted of procedural costs (staff costs, consumables, red blood cell units), chelation costs, and costs associated with SCD complications (stroke and emergency admissions). The modelled populations comprised of 12 different subgroups, based on patient age, indication and requirement for chelation; these were not combined into a single estimate of costs saved and budgetary impact assuming a particular case mix. In all subgroups of the base case, Spectra Optia was less costly than manual RBCx, and less costly than top up transfusion in half the scenarios. The sponsor provided extensive deterministic sensitivity analysis and using this reported that Spectra Optia was cost saving in the large majority of plausible scenarios.

The EAC critiqued the company's model and identified several areas of uncertainty. Of primary concern was inclusion in the model of clinical event rates for chelation requirements, stroke and hospital readmission, that were not substantiated by robust published clinical evidence. Although both the EAC's clinical experts and the company's clinical advisors were unanimous that automated RBCx could plausibly reduce ferritin levels, the EAC considered that the extent of this could not be quantified or reliably modelled to chelation requirement. A second major concern was that the company had not included the capital or maintenance costs of the Spectra Optia system in the model.

The EAC reproduced the sponsor's model and performed additional analysis using the sponsor's model and additional unpublished information from NHS sources. This model included capital and maintenance costs of the Spectra Optia system, as well as revised estimates for the cost of management of iron overload and procedures, but retained the company's assumptions and estimates regarding clinical event rates. Using these revisions, the EAC found that the Spectra Optia was potentially cost saving in patients with no or mild iron overload, but potentially cost incurring in patients who have moderate or severe overload compared with use of manual RBCx (Table 4.13). It should be emphasised that these results are subject to the same uncertainty as those of the company, but if the underlying clinical assumptions of the model are correct they give credence to the cost-saving potential of the Spectra Optia system in certain patient groups.

In summary, the EAC considered that the uncertainty around key parameters used in the company submission, was such that it was not possible to establish, with complete confidence, the clinical superiority or cost saving

potential of the Spectra Optia system compared with manual RBCx. However, it should be emphasised that this was because there was a lack of sufficient quality published evidence to support the incremental benefits of automated RBCx over manual RBCx, particularly concerning clinical outcomes, rather than evidence of no benefit. It is important to consider that anecdotal evidence from clinical experts is supportive of the Spectra Optia system and they believe it is likely that the technology does offer real clinical benefits over manual RBCx, including a reduced requirement for chelation. The EAC noted that iron overload in SCD patients is an important cause of morbidity and mortality [81], and many of the associated costs with iron overload, such as monitoring with MRI and treatment of complications, such as heart failure and liver cirrhosis, were not included in the model. Thus, even small improvements in the management of iron overload could lead to substantial cost savings that might be expected to result in cost savings overall. This is also true for the prevention of stroke and other vaso-occlusive crises.

Whilst there is also a lack of published evidence that the Spectra Optia system has improved safety compared with manual RBCx, it seems self-evident that a fully automated system will reduce human error and produce more predictable outcomes than a manual system. The Spectra Optia system also has the potential to standardise clinical practice at a national level. This is important considering the current geographical inequalities that exist in the provision of treatment for SCD [34]. Currently, patients from low prevalence areas may be faced with the inconvenience and cost of travelling to specialist centres elsewhere. There may be the possibility that these patients could access Spectra Optia through specialised care service such as TAS (Section 4.5.3), and therefore if the Spectra Optia device were adopted, it is possible these inequalities could be addressed.

6 Implications for research

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. Whilst 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 undertaken in the future. This is because there is a lack of clinical equipoise; that is, whilst there is no real uncertainty that Spectra Optia is at least as clinically effective as manual RBCx, it also 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 RBCx. The expert advisors to the EAC were unanimous on this issue (see EAC Correspondence Log).

With no prospective comparative research forthcoming, the EAC considers that the most appropriate methodology to address the shortcomings in evidence would be the development of a registry. To be genuinely informative, this would need to be a disease registry that included data on comparative methods of treatment, such as manual and partial RBCx, and top up transfusions. Development of the National Haemoglobinopathy Registry (NHR) may be a possibility.

The NHR is a database of patients with red cell disorders (mainly sickle cell disease and thalassaemia major) living in the UK. The first NHR Annual Report (2013-14) was published in September 2014; therefore the latest public release of 2014-15 data may be published imminently.

The NHR was established with first patient data entry around October 2008 and the numbers of sickle cell patients registered is approaching 10,000 at August 2015. It collects data which are required by NHS England from Specialist Haemoglobinopathy Centres. The central aim of the registry is to improve patient care and an Annual Review process commenced in 2014-15, requiring all patients to have a comprehensive annual clinical consultation and review of all aspects of their health and care.

The 2013-14 NHR Annual Report notes that accurate figures on patients receiving blood transfusion therapy and types of chelation therapy are not easily available at the majority of centres, but this is a key area for both quality improvement and service planning. Indeed, the implementation of the Annual Review of patients from 2014-15 is intended to allow accurate data to be obtained on numbers of patients being transfused, method of transfusion, type of iron chelation and efficacy of iron chelation (by reviewing markers of iron overload) [82].

Thus there is the potential to explore the feasibility of future observational research using NHR data on sickle cell patients. An NHR Steering Committee considers such proposals for the interpretation of epidemiological data [83]. The EAC notes that these chapter authors are also NICE-ratified clinical experts, who contributed answers to the EAC's questions during this assessment of Spectra Optia. This may help facilitate a collaborative approach to such future research using registry data.

Subsequent to the above potential observational research using NHR registry data, it may then become plausible to create an economic model with robust clinical and resource usage inputs for both Spectra Optia and its real-world comparators.

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Appendix A - System comparison of Cobe Spectra versus Spectra Optia

Summarised from the manufacturer's website:

http://advancingapheresis-emea.terumobct.com/compare-systems

Cobe Spectra	Spectra Optia
USABILITY	
Same colour for clamps and roller clamps Saline & AC lines are the same thickness Push button panel, LED display Limited blood prime Troubleshooting using user manual Single-line LED displays procedure information	Colour-coded clamps, roller clamps & lines A portion of the saline line is thicker to distinguish it from the AC line Intuitive touch screen graphical user interface display Dedicated custom prime (red blood cell or albumin) Onscreen troubleshooting High-resolution screen displays the right information at the right time
MOBILITY	
177kg 149cm High x 70cm Wide x 71cm Deep Swivel-screen for moving Stationary IV pole Narrow wheels with unidirectional movement	92kg 106cm High x 53cm Wide x 81cm Deep Fold-down screen for moving & storage Telescoping IV pole Large wheels on pivoting casters
EFFICIENCY	

A dedicated tubing set for each protocol Multiple steps to load the tubing set Navigation through multiple screens to access desired data Manually recorded data Minimal data storage capabilities Manual data calculations Standalone tube sealer Requires 0.5m^2 floor space	Tubing sets can be used for multiple protocols Tubing set with cassette that loads in a few steps Minimal screen navigation to access desired data Automatically recorded data, which can then be printed or exported as a PDF Access to protocol data for up to 100 procedures Automated data calculations Incorporated tube sealer Requires 0.4m^2 floor space
CONSISTENCY	
Manual interface management required to monitor interface levels Accurate fluid balance; not cumulative if changed during run Consistent flow rates	Automated interface management (AIM) with operator control, plus option to manually monitor the interface Accurate fluid balance, cumulative during run; includes custom prime, blood warmer and rinseback Consistent flow rates even at lower speeds
PROTOCOLS – RED BLOOD CELL EXCHANGE	
Multiple screens to navigate through to access the data you need Complex procedure Blood prime not differentiated from the procedure Extracorporeal volume (ECV) = 285ml[1]	Streamlines your procedure management and automates the calculations Streamlined work flow Clearly defined custom prime sequence that differentiates priming from the run targets ECV = 185ml[1]

[1] Tormey CA, *et al*., Improved Plasma Removal Efficiency for Therapeutic Plasma Exchange Using a New Apheresis Platform. Transfusion 2010; 50(2): 471-477

Appendix B - Literature search strategies

A.1: Source: MEDLINE <1946 to June Week 2 2015>

Interface / URL: Ovid
Search date: 19/06/15
Retrieved records: 59
Search strategy:

1 Anemia, Sickle Cell/ (17346)
2 sickle cell.tw. (17302)
3 1 or 2 (21130)
4 Erythrocyte Transfusion/ (6749)
5 ((red blood cell* or erythrocyte*) adj2 (exchang* or transfusion*)).tw. (3808)
6 (red cell* adj2 (exchang* or transfusion*)).tw. (1518)
7 erythrocytapheresis.tw. (144)
8 apheresis.tw. (4915)
9 or/4-8 (14676)
10 (terumo or optia or spectra or Cobe Spectra system or manual or automat*).tw. (286527)
11 3 and 9 and 10 (59)

A.2: Source: MEDLINE In-Process & Other Non-Indexed Citations June 18, 2015

Interface / URL: OvidSP
Search date: 19/06/15
Retrieved records: 4
Search strategy:

1 sickle cell.tw. (1230)
2 ((red blood cell* or erythrocyte*) adj2 (exchang* or transfusion*)).tw. (342)
3 (red cell* adj2 (exchang* or transfusion*)).tw. (87)
4 erythrocytapheresis.tw. (6)
5 apheresis.tw. (318)
6 (terumo or optia or spectra or Cobe Spectra system or manual or automat*).tw. (61536)
7 2 or 3 or 4 or 5 (742)
8 1 and 6 and 7 (4)

A.3: Source: Embase <1974 to 2015 June 18>

Interface / URL: OvidSP
Search date: 19/06/15
Retrieved records: 136
Search strategy:

1 sickle cell.tw. (24149)

2 sickle cell anemia/ (26356)
3 ((red blood cell* or erythrocyte*) adj2 (exchang* or transfusion*)).tw. (6197)
4 (red cell* adj2 (exchang* or transfusion*)).tw. (2591)
5 erythrocytapheresis.tw. (227)
6 apheresis.tw. (9898)
7 erythrocyte transfusion/ (16228)
8 apheresis/ (10115)
9 apheresis device/ (192)
10 (terumo or optia or spectra or Cobe Spectra system or manual or automat*).tw. (405110)
11 1 or 2 (30575)
12 or/3-8 (32365)
13 9 or 10 (405182)
14 11 and 12 and 13 (136)

A.4: Source: Scopus

Interface / URL: http://www.scopus.com/
Search date: 19/06/15
Retrieved records: 11
Search strategy:

(TITLE-ABS-KEY ("sickle cell") AND TITLE-ABS-KEY (("red blood cell*" W/2 exchang*) OR ("red blood cell*" W/2 transfusion*) OR ("red cell*" W/2 exchang*) OR ("red cell*" W/2 transfusion*) OR (erythrocyte* W/2 exchang*) OR (erythrocyte* W/2 transfusion*) OR apheresis OR erythrocytapheresis) AND TITLE-ABS-KEY (terumo OR optia OR spectra OR Cobe Spectra system OR manual OR automated*))

A.5: Source: The Cochrane Library

Interface / URL: Cochrane Library / Wiley Interscience
Search date: 19/06/15
Retrieved records: 5
Search strategy:

Line 1 built in the Advanced Interface, then added to Search Manager:

#1 terumo or optia or spectra or Cobe or automat* or manual:ti,ab,kw and "sickle cell":ti,ab,kw and erythrocytapheresis or apheresis or "exchange transfusion" or blood or erythrocyte* or "red cell":ti,ab,kw (Word variations have been searched) 5
#2 #1 in Cochrane Reviews (Reviews and Protocols) 1
#3 #1 in Other Reviews 0
#4 #1 in Trials 3
#5 #1 in Technology Assessments 0
#6 #1 in Economic Evaluations 1

Note: For the purpose of re-running the search, it has been assumed that where the sponsor stated that they searched “Cochrane Library (all relevant components”) (page 174), this meant they searched CDSR, CENTRAL, DARE, HTA Database and NHS EED

A.6: Source: Econlit 1886 to May 2015

Interface / URL: OvidSP
Search date: 19/06/15
Retrieved records: 0
Search strategy:

1 (terumo or optia or spectra or Cobe or automat* or manual).af. 5923
2 (erythrocytapheresis or apheresis or exchange transfusion or blood or erythrocyte* or red cell).af. 548
3 sickle cell.af. 6
4 1 and 2 and 3 0

Note: this translation assumes that the sponsor searched Econlit using the EBSCO interface.

A.7: Source: Science Citation Index Expanded (SCI-EXPANDED) --1900-present / Conference Proceedings Citation Index- Science (CPCI-S) --1990-present

Interface / URL: Web of Science
Search date: 19/06/15
Retrieved records: 82
Search strategy:

TS=(terumo or optia or spectra or Cobe or automat* or manual) AND TS=(("red blood cell*" NEAR/2 exchang*) OR ("red blood cell*" NEAR/2 transfusion*) OR (“red cell*” NEAR/2 exchang*) OR (“red cell*” NEAR/2 transfusion*) OR (erythrocyte* NEAR/2 exchang*) OR (erythrocyte* NEAR/2 transfusion*) OR *apheresis OR "exchange transfusion") AND TS=("sickle cell")

Indexes=SCI-EXPANDED, CPCI-S Timespan=All years

A.8: Source: Pubmed

Interface / URL: http://www.ncbi.nlm.nih.gov/pubmed
Search date: 19/06/15
Retrieved records: 8
Search strategy:

#1 Search pubstatusaheadofprint AND (terumo OR optia OR spectra OR Cobe OR apheresis OR erythrocytapheresis OR manual OR automat*) AND "sickle cell" 8

Search strategies: sponsor search 2

A.9: Source: MEDLINE(R) 1946 to June Week 2 2015

Interface / URL: OvidSP
Search date: 22/06/15
Retrieved records: 67
Search strategy:

1 Anemia, Sickle Cell/ (17346)
2 sickle cell.tw. (17302)
3 1 or 2 (21130)
4 Erythrocyte Transfusion/ (6749)
5 ((red blood cell* or erythrocyte*) adj2 (exchang* or transfusion*)).tw. (3808)
6 (red cell* adj2 (exchang* or transfusion*)).tw. (1518)
7 erythrocytapheresis.tw. (144)
8 apheresis.tw. (4915)
9 4 or 5 or 6 or 7 or 8 (14676)
10 (terumo or optia or spectra or Cobe or manual or automat*).tw. (286723)
11 3 and 9 and 10 (59)
12 3 and 9 (497)
13 (exchang* or erythrocytapheres* or automat* or manual).tw. (374752)
14 12 and 13 (159)
15 14 not 11 (100)
16 transfus*.tw. (81891)
17 3 and 9 and 16 (381)
18 14 and 16 (105)
19 18 not 11 (67)
20 15 and 19 (67)

A.10: Source: MEDLINE(R) In-Process & Other Non-Indexed Citations June 19, 2015

Interface / URL: OvidSP
Search date: 22/06/15
Retrieved records: 6
Search strategy:

1 sickle cell.tw. (1231)
2 ((red blood cell* or erythrocyte*) adj2 (exchang* or transfusion*)).tw. (344)
3 (red cell* adj2 (exchang* or transfusion*)).tw. (87)
4 erythrocytapheresis.tw. (6)
5 apheresis.tw. (318)

6 (terumo or optia or spectra or Cobe or manual or automat*).tw. (61605)
7 2 or 3 or 4 or 5 (744)
8 1 and 6 and 7 (4)
9 (exchang* or erythrocytapheres* or automat* or manual).tw. (49884)
10 1 and 7 and 9 (10)
11 10 not 8 (6)

A.11: Source: Embase 1974 to 2015 June 19

Interface / URL: OvidSP
Search date: 22/06/15
Retrieved records: 206
Search strategy:

1 sickle cell.tw. (24157)
2 sickle cell anemia/ (26364)
3 ((red blood cell* or erythrocyte*) adj2 (exchang* or transfusion*)).tw. (6199)
4 (red cell* adj2 (exchang* or transfusion*)).tw. (2591)
5 erythrocytapheresis.tw. (227)
6 apheresis.tw. (9900)
7 erythrocyte transfusion/ (16236)
8 apheresis/ (10115)
9 apheresis device/ (192)
10 (terumo or optia or spectra or Cobe or manual or automat*).tw. (405620)
11 1 or 2 (30586)
12 or/3-8 (32377)
13 9 or 10 (405692)
14 11 and 12 and 13 (136)
15 (exchang* or erythrocytapheres* or automat* or manual).tw. (514698)
16 9 or 15 (514826)
17 11 and 12 and 16 (340)
18 17 not 14 (206)

A.12: Source: The Cochrane Library

Interface / URL: The Cochrane Library / Wiley Interscience
Search date: 22/06/15
Retrieved records: 19
Search strategy:

#1 "sickle cell":ti,ab,kw and exchang* or erythrocytapheres* or automat* or manual:ti,ab,kw (Word variations have been searched) 23
#2 terumo or optia or spectra or Cobe or automat* or manual:ti,ab,kw and "sickle cell":ti,ab,kw and erythrocytapheresis or apheresis or "exchange transfusion" or blood or erythrocyte* or "red cell":ti,ab,kw (Word variations have been searched) 5
#3 #1 not #2 19
#4 #3 in Cochrane Reviews (Reviews and Protocols) 2

#5 #3 in Other Reviews 0
#6 #3 in Trials 16
#7 #3 in Technology Assessments 0
#8 #3 in Economic Evaluations 1

Notes:

1. For the purpose of re-running the search, it has been assumed that where the sponsor stated that they searched “Cochrane Library (all relevant components”) (page 176), this meant they searched CDSR, CENTRAL, DARE, HTA Database and NHS EED

2. The search as reported in the sponsor submission (page 176) appears to include an error in line 2:

*erythrocytapheresis or apheresis or **3**"exchange transfusion" or blood or erythrocyte* or "red cell"*

It is not clear if this is a reporting / typographical error, or if the error was included in the sponsor search when run. For the purposes of re-running the search, this error was removed.

A.13: Source: Pubmed

Interface / URL: http://www.ncbi.nlm.nih.gov/pubmed
Interface / URL:
Search date: 22/06/15
Retrieved records: 2
Search strategy:

#3 Search (#1 NOT #2) 2

#2 Search (pubstatusaheadofprint AND (terumo OR optia OR spectra OR Cobe OR apheresis OR erythrocytapheresis OR manual OR automat*) AND "sickle cell") 8

#1 Search pubstatusaheadofprint AND (exchang* or erythrocytapheres* or automat* or manual) AND "sickle cell" 9

A.14: Source: Econlit 1886 to May 2015

Interface / URL: OvidSP
Search date: 22/06/15
Retrieved records: 0
Search strategy:

1	(sickle cell and (exchang* or erythrocytapheres* or automat* or manual)).ab.	0
2	(sickle cell and (exchang* or erythrocytapheres* or automat* or manual)).ti.	0
3	1 or 2	0

Appendix C - EAC Additional Clinical Evidence Searches

Literature Search Results

The searches identified 2745 records (Table 1). Following deduplication 1361 records were assessed for relevance.

Table 1: Literature search results

Resource	Records identified
MEDLINE In-Process & Other Non-Indexed Citations and MEDLINE 1946 to Present	622
Embase	1096
Cochrane Central Register of Controlled Trials	42
Database of Abstracts of Reviews of Effect	7
Health Technology Assessment Database	4
NHS Economic Evaluation Database	12
Cochrane Database of Systematic Reviews	17
PubMed	87
Science Citation Index Expanded (SCI-EXPANDED) / Conference Proceedings Citation Index- Science (CPCI-S)	690
Econlit	10
HEED: Health Economic Evaluations Database	9
CEA Registry	0
Clinicaltrials.gov	80
WHO International Clinical Trials Registry Platform	37
ISRCTN registry	3
British Society of Haematology website	0
Royal College of Pathologists website	0
Rare Disease UK website	0
UK Forum on Haemoglobin Disorders website	6
Action for Sick Children website	0
African Caribbean Leukaemia Trust website	0
Bliss website	0
Different Strokes website	0
Ethnic Health Foundation website	0
National Childbirth Trust website	0
Sickle Cell and Young Stroke Survivors website	0
Sickle Cell Society website	1
Specialised Healthcare Alliance website	0
Stroke Association website	0
Together for Short Lives website	2
Tommy's website	0
Abstracts from the American Society for Apheresis 36th	14

Annual Meeting, 2015	
Abstracts of the 55th Annual Scientific Meeting of the British Society for Haematology, 2015	3
Abstracts of the 54th Annual Scientific Meeting of the British Society for Haematology, 2014	1
Abstracts of the 53rd Annual Scientific Meeting of the British Society for Haematology, 2013	2
TOTAL	**2745**
TOTAL after deduplication (within-set, and against the re-run sponsor searches)	**1361**

Search strategies: EAC additional clinical evidence

B.1: Source: MEDLINE(R) In-Process & Other Non-Indexed Citations and MEDLINE(R) 1946 to Present

Interface / URL: OvidSP
Search date: 02/0715
Retrieved records: 622
Search strategy:

1 anemia, sickle cell/ (17359)
2 sickle cell$1.ti,ab,kf. (19260)
3 (SCA or SCD).ti,ab,kf. (11679)
4 (h?emoglobin S or h?emoglobin SS or SS disease$1).ti,ab,kf. (1774)
5 (HBS or HB-S or HBSS or HB-SS).ti,ab,kf. (10918)
6 Hemoglobin, Sickle/ (2754)
7 (h?emoglobin adj3 thalass?emia).ti,ab,kf. (768)
8 (sickle adj3 (an?emia$ or h?emoglobin)).ti,ab,kf. (8190)
9 Hemoglobin SC Disease/ (572)
10 (h?emoglobin SC or SC disease$1).ti,ab,kf. (397)
11 (HBSC or HB-SC).ti,ab,kf. (654)
12 (h?emoglobin SD or SD disease$1).ti,ab,kf. (153)
13 (HBSD or HB-SD).ti,ab,kf. (29)
14 sickling.ti,ab,kf. (1287)
15 (drepanocyt$ or microdrepanocyt$).ti,ab,kf. (363)
16 meniscocyt$.ti,ab,kf. (3)
17 or/1-16 (41804)
18 Exchange Transfusion, Whole Blood/ (4140)
19 Erythrocyte Transfusion/ (6760)
20 blood component removal/ (3834)
21 ((red blood cell or red blood cells or red cell or red cells) adj3 exchang$).ti,ab,kf. (472)
22 ((RBC or RBCs or RC or RCs) adj3 exchang$).ti,ab,kf. (96)
23 ((erythrocyte$ or normocyte$) adj3 exchang$).ti,ab,kf. (476)
24 (RBCX or RBCE or RCX or RCE).ti,ab,kf. (408)

25 (ARCET or RCET).ti,ab,kf. (10)
26 erythroexchange$1.ti,ab,kf. (6)
27 erythrocytapheresis.ti,ab,kf. (150)
28 (exchang$ adj3 (transfusion$1 or blood)).ti,ab,kf. (5925)
29 (EBT or EBTs).ti,ab,kf. (770)
30 ((chronic or exsanguinatio$ or substitution or total or replacement) adj transfusion$1).ti,ab,kf. (533)
31 cytapheresis/ (302)
32 (apheresis or cytapheresis or cytopheresis or pheresis).ti,ab,kf. (5795)
33 ((automat$ or auto) adj3 exchang$).ti,ab,kf. (266)
34 (blood cell$1 adj3 (separator$1 or separation or separating)).ti,ab,kf. (545)
35 (optia$ or cobe$ or terumo$ or caridian$ or gambro$).ti,ab,kf. (1603)
36 ((spectra or spectrar or spectratm or spectrartm) and (exchang$ or transfusion$1)).ti,ab,kf. (5663)
37 (manual$ adj3 exchang$).ti,ab,kf. (64)
38 or/18-37 (31395)
39 17 and 38 (975)
40 exp animals/ not humans/ (4063890)
41 (news or comment or editorial).pt. (1050549)
42 39 not (40 or 41) (935)
43 limit 42 to (english language and yr="1993 -Current") (640)
44 remove duplicates from 43 (622)

B.2: Source: Embase 1974 to 1974 to 2015 July 01

Interface / URL: OvidSP
Search date: 02/07/15
Retrieved records: 1096
Search strategy:

1 *sickle cell anemia/ or *sickle cell crisis/ (19312)
2 sickle cell$1.ti,ab,kw. (24755)
3 (SCA or SCD).ti,ab,kw. (19078)
4 (SCA or SCD).ti,ab,kw. (19078)
5 (h?emoglobin S or h?emoglobin SS or SS disease$1).ti,ab,kw. (2333)
6 (HBS or HB-S or HBSS or HB-SS).ti,ab,kw. (15347)
7 *hemoglobin S/ (1901)
8 *sickle cell beta thalassemia/ (95)
9 (h?emoglobin adj3 thalass?emia).ti,ab,kw. (958)
10 (sickle adj3 (an?emia$ or h?emoglobin)).ti,ab,kw. (9563)
11 *hemoglobin SC disease/ (280)
12 (h?emoglobin SC or SC disease$1).ti,ab,kw. (534)
13 (HBSC or HB-SC).ti,ab,kw. (928)
14 *hemoglobin SD disease/ (9)
15 (h?emoglobin SD or SD disease$1).ti,ab,kw. (342)
16 (HBSD or HB-SD).ti,ab,kw. (61)

17 sickling.ti,ab,kw. (1742)
18 (drepanocyt$ or microdrepanocyt$).ti,ab,kw. (426)
19 meniscocyt$.ti,ab,kw. (3)
20 or/1-19 (55445)
21 *exchange blood transfusion/ (2481)
22 *erythrocyte transfusion/ (3380)
23 *apheresis/ (4268)
24 ((red blood cell or red blood cells or red cell or red cells) adj3 exchang$).ti,ab,kw. (668)
25 ((RBC or RBCs or RC or RCs) adj3 exchang$).ti,ab,kw. (160)
26 ((erythrocyte$ or normocyte$) adj3 exchang$).ti,ab,kw. (505)
27 (RBCX or RBCE or RCX or RCE).ti,ab,kw. (587)
28 (ARCET or RCET).ti,ab,kw. (12)
29 erythroexchange$1.ti,ab,kw. (6)
30 erythrocytapheresis.ti,ab,kw. (239)
31 (exchang$ adj3 (transfusion$1 or blood)).ti,ab,kw. (7094)
32 (EBT or EBTs).ti,ab,kw. (1047)
33 ((chronic or exsanguinatio$ or substitution or total or replacement) adj transfusion$1).ti,ab,kw. (933)
34 *cytapheresis/ (343)
35 (apheresis or cytapheresis or cytopheresis or pheresis).ti,ab,kw. (10931)
36 ((automat$ or auto) adj3 exchang$).ti,ab,kw. (354)
37 (blood cell$1 adj3 (separator$1 or separation or separating)).ti,ab,kw. (688)
38 apheresis device/ (197)
39 (optia$ or cobe$ or terumo$ or caridian$ or gambro$).ti,ab,kw,dv,dm. (6764)
40 ((spectra or spectrar or spectratm or spectrartm) and (exchang$ or transfusion$1)).ti,ab,kw. (5675)
41 (spectra or spectrar or spectratm or spectrartm).dv,dm. (586)
42 (manual$ adj3 exchang$).ti,ab,kw. (100)
43 or/21-42 (38538)
44 20 and 43 (1371)
45 (animal/ or animal experiment/ or animal model/ or animal tissue/ or nonhuman/) not exp human/ (5171609)
46 editorial.pt. (482630)
47 44 not (45 or 46) (1351)
48 limit 47 to (english language and yr="1993 -Current") (1109)
49 remove duplicates from 48 (1096)

B.3: Source: Cochrane Central Register of Controlled Trials: Issue 6 of 12, June 2015

Interface / URL: Cochrane Library / Wiley
Search date: 02/07/15
Retrieved records: 42
Search strategy:

#1 [mh ^"anemia, sickle cell"] 371
#2 (sickle next cell*) 1141
#3 (SCA or SCD) 616
#4 (h*emoglobin next S or h*emoglobin next SS or SS next disease*) 92
#5 (HBS or HB-S or HBSS or HB-SS) 824
#6 [mh ^"Hemoglobin, Sickle"] 18
#7 (h*emoglobin near/3 thalass*emia) 35
#8 (sickle near/3 (an*emia* or h*emoglobin)) 712
#9 [mh ^"Hemoglobin SC Disease"] 15
#10 (h*emoglobin next SC or SC next disease*) 46
#11 (HBSC or HB-SC) 41
#12 (h*emoglobin next SD or SD next disease*) 30
#13 (HBSD or HB-SD) 7
#14 sickling 58
#15 (drepanocyt* or microdrepanocyt*) 42
#16 meniscocyt* 5
#17 {or #1-#16} 2281
#18 [mh ^"Exchange Transfusion, Whole Blood"] 68
#19 [mh ^"Erythrocyte Transfusion"] 518
#20 [mh ^"blood component removal"] 199
#21 (("red blood cell" or "red blood cells" or "red cell" or "red cells") near/3 exchang*) 10
#22 ((RBC or RBCs or RC or RCs) near/3 exchang*) 4
#23 ((erythrocyte* or normocyte*) near/3 exchang*) 21
#24 (RBCX or RBCE or RCX or RCE) 36
#25 (ARCET or RCET) 0
#26 erythroexchange* 0
#27 erythrocytapheresis 23
#28 (exchang* near/3 (transfusion* or blood)) 487
#29 (EBT or EBTs) 58
#30 ((chronic or exsanguinatio* or substitution or total or replacement) next transfusion*) 89
#31 [mh ^cytapheresis] 13
#32 (apheresis or cytapheresis or cytopheresis or pheresis) 823
#33 ((automat* or auto) near/3 exchang*) 4
#34 (("blood cell" or "blood cells") near/3 (separator* or separation or separating)) 43
#35 (optia* or cobe* or terumo* or caridian* or gambro*) 410
#36 ((spectra or spectrar or spectratm or spectrartm) and (exchang* or transfusion*)) 54
#37 (manual* near/3 exchang*) 9
#38 {or #18-#37} 2434
#39 #17 and #38 Publication Year from 1993 to 2015 72
#40 #39 in Trials 42

B.4: Source: Database of Abstracts of Reviews of Effects: Issue 2 of 4, April 2015

Interface / URL: Cochrane Library / Wiley
Search date: 02/07/15
Retrieved records: 7
Search strategy:

#1 [mh ^"anemia, sickle cell"] 371
#2 (sickle next cell*) 1141
#3 (SCA or SCD) 616
#4 (h*emoglobin next S or h*emoglobin next SS or SS next disease*) 92
#5 (HBS or HB-S or HBSS or HB-SS) 824
#6 [mh ^"Hemoglobin, Sickle"] 18
#7 (h*emoglobin near/3 thalass*emia) 35
#8 (sickle near/3 (an*emia* or h*emoglobin)) 712
#9 [mh ^"Hemoglobin SC Disease"] 15
#10 (h*emoglobin next SC or SC next disease*) 46
#11 (HBSC or HB-SC) 41
#12 (h*emoglobin next SD or SD next disease*) 30
#13 (HBSD or HB-SD) 7
#14 sickling 58
#15 (drepanocyt* or microdrepanocyt*) 42
#16 meniscocyt* 5
#17 {or #1-#16} 2281
#18 [mh "Blood Transfusion"] 3361
#19 [mh ^"blood component removal"] 199
#20 (("red blood cell" or "red blood cells" or "red cell" or "red cells") near/3 exchang*) 10
#21 ((RBC or RBCs or RC or RCs) near/3 exchang*) 4
#22 ((erythrocyte* or normocyte*) near/3 exchang*) 21
#23 (RBCX or RBCE or RCX or RCE) 36
#24 (ARCET or RCET) 0
#25 erythroexchange* 0
#26 erythrocytapheresis 23
#27 (exchang* near/3 blood) 367
#28 (EBT or EBTs) 58
#29 transfusion* 10363
#30 [mh ^cytapheresis] 13
#31 (apheresis or cytapheresis or cytopheresis or pheresis) 823
#32 ((automat* or auto) near/3 exchang*) 4
#33 (("blood cell" or "blood cells") near/3 (separator* or separation or separating)) 43
#34 (optia* or cobe* or terumo* or caridian* or gambro*) 410
#35 ((spectra or spectrar or spectratm or spectrartm) and exchang*) 16
#36 (manual* near/3 exchang*) 9

#37 {or #18-#36} 11723
#38 #17 and #37 Publication Year from 1993 to 2015 303
#39 #38 in Other Reviews 7

B.5: Source: NHS Economic Evaluation Database: Issue 2 of 4, April 2015

Interface / URL: Cochrane Library / Wiley
Search date: 02/07/15
Retrieved records: 12
Search strategy:

#1 [mh ^"anemia, sickle cell"] 371
#2 (sickle next cell*) 1141
#3 (SCA or SCD) 616
#4 (h*emoglobin next S or h*emoglobin next SS or SS next disease*) 92
#5 (HBS or HB-S or HBSS or HB-SS) 824
#6 [mh ^"Hemoglobin, Sickle"] 18
#7 (h*emoglobin near/3 thalass*emia) 35
#8 (sickle near/3 (an*emia* or h*emoglobin)) 712
#9 [mh ^"Hemoglobin SC Disease"] 15
#10 (h*emoglobin next SC or SC next disease*) 46
#11 (HBSC or HB-SC) 41
#12 (h*emoglobin next SD or SD next disease*) 30
#13 (HBSD or HB-SD) 7
#14 sickling 58
#15 (drepanocyt* or microdrepanocyt*) 42
#16 meniscocyt* 5
#17 {or #1-#16} 2281
#18 [mh "Blood Transfusion"] 3361
#19 [mh ^"blood component removal"] 199
#20 (("red blood cell" or "red blood cells" or "red cell" or "red cells") near/3 exchang*) 10
#21 ((RBC or RBCs or RC or RCs) near/3 exchang*) 4
#22 ((erythrocyte* or normocyte*) near/3 exchang*) 21
#23 (RBCX or RBCE or RCX or RCE) 36
#24 (ARCET or RCET) 0
#25 erythroexchange* 0
#26 erythrocytapheresis 23
#27 (exchang* near/3 blood) 367
#28 (EBT or EBTs) 58
#29 transfusion* 10363
#30 [mh ^cytapheresis] 13
#31 (apheresis or cytapheresis or cytopheresis or pheresis) 823
#32 ((automat* or auto) near/3 exchang*) 4

#33 (("blood cell" or "blood cells") near/3 (separator* or separation or separating)) 43
#34 (optia* or cobe* or terumo* or caridian* or gambro*) 410
#35 ((spectra or spectrar or spectratm or spectrartm) and exchang*) 16
#36 (manual* near/3 exchang*) 9
#37 {or #18-#36} 11723
#38 #17 and #37 Publication Year from 1993 to 2015 303
#39 #38 in Other Reviews 7
#40 #38 in Technology Assessments 4
#41 #38 in Economic Evaluations 12

B.6: Source: Health Technology Assessment Database : Issue 2 of 4, April 2015

Interface / URL: Cochrane Library / Wiley
Search date: 02/07/15
Retrieved records: 4
Search strategy:

#1 [mh ^"anemia, sickle cell"] 371
#2 (sickle next cell*) 1141
#3 (SCA or SCD) 616
#4 (h*emoglobin next S or h*emoglobin next SS or SS next disease*) 92
#5 (HBS or HB-S or HBSS or HB-SS) 824
#6 [mh ^"Hemoglobin, Sickle"] 18
#7 (h*emoglobin near/3 thalass*emia) 35
#8 (sickle near/3 (an*emia* or h*emoglobin)) 712
#9 [mh ^"Hemoglobin SC Disease"] 15
#10 (h*emoglobin next SC or SC next disease*) 46
#11 (HBSC or HB-SC) 41
#12 (h*emoglobin next SD or SD next disease*) 30
#13 (HBSD or HB-SD) 7
#14 sickling 58
#15 (drepanocyt* or microdrepanocyt*) 42
#16 meniscocyt* 5
#17 {or #1-#16} 2281
#18 [mh "Blood Transfusion"] 3361
#19 [mh ^"blood component removal"] 199
#20 (("red blood cell" or "red blood cells" or "red cell" or "red cells") near/3 exchang*) 10
#21 ((RBC or RBCs or RC or RCs) near/3 exchang*) 4
#22 ((erythrocyte* or normocyte*) near/3 exchang*) 21
#23 (RBCX or RBCE or RCX or RCE) 36
#24 (ARCET or RCET) 0
#25 erythroexchange* 0
#26 erythrocytapheresis 23

#27 (exchang* near/3 blood) 367
#28 (EBT or EBTs) 58
#29 transfusion* 10363
#30 [mh ^cytapheresis] 13
#31 (apheresis or cytapheresis or cytopheresis or pheresis) 823
#32 ((automat* or auto) near/3 exchang*) 4
#33 (("blood cell" or "blood cells") near/3 (separator* or separation or separating)) 43
#34 (optia* or cobe* or terumo* or caridian* or gambro*) 410
#35 ((spectra or spectrar or spectratm or spectrartm) and exchang*) 16
#36 (manual* near/3 exchang*) 9
#37 {or #18-#36} 11723
#38 #17 and #37 Publication Year from 1993 to 2015 303
#39 #38 in Other Reviews 7
#40 #38 in Technology Assessments 4

B.7: Source: Cochrane Database of Systematic Reviews: Issue 7 of 12, July 2015

Interface / URL: Cochrane Library / Wiley
Search date: 02/07/15
Retrieved records: 17
Search strategy:

#1 [mh ^"anemia, sickle cell"] 371
#2 (sickle next cell*):ti,ab,kw 944
#3 (SCA or SCD):ti,ab,kw 511
#4 (h*emoglobin next S or h*emoglobin next SS or SS next disease*):ti,ab,kw 51
#5 (HBS or HB-S or HBSS or HB-SS):ti,ab,kw 739
#6 [mh ^"Hemoglobin, Sickle"] 18
#7 (h*emoglobin near/3 thalass*emia):ti,ab,kw 13
#8 (sickle near/3 (an*emia* or h*emoglobin)):ti,ab,kw 635
#9 [mh ^"Hemoglobin SC Disease"] 15
#10 (h*emoglobin next SC or SC next disease*):ti,ab,kw 21
#11 (HBSC or HB-SC):ti,ab,kw 13
#12 (h*emoglobin next SD or SD next disease*):ti,ab,kw 18
#13 (HBSD or HB-SD):ti,ab,kw 1
#14 sickling:ti,ab,kw 34
#15 (drepanocyt* or microdrepanocyt*):ti,ab,kw 31
#16 meniscocyt*:ti,ab,kw 0
#17 {or #1-#16} 1956
#18 [mh "Blood Transfusion"] 3361
#19 [mh ^"blood component removal"] 199
#20 (("red blood cell" or "red blood cells" or "red cell" or "red cells") near/3 exchang*):ti,ab,kw 5

#21 ((RBC or RBCs or RC or RCs) near/3 exchang*):ti,ab,kw 2
#22 ((erythrocyte* or normocyte*) near/3 exchang*):ti,ab,kw 21
#23 (RBCX or RBCE or RCX or RCE):ti,ab,kw 23
#24 (ARCET or RCET):ti,ab,kw 0
#25 erythroexchange*:ti,ab,kw 0
#26 erythrocytapheresis:ti,ab,kw 18
#27 (exchang* near/3 blood):ti,ab,kw 236
#28 (EBT or EBTs):ti,ab,kw 47
#29 transfusion*:ti,ab,kw 8370
#30 [mh ^cytapheresis] 13
#31 (apheresis or cytapheresis or cytopheresis or pheresis):ti,ab,kw 592
#32 ((automat* or auto) near/3 exchang*):ti,ab,kw 2
#33 (("blood cell" or "blood cells") near/3 (separator* or separation or separating)):ti,ab,kw 37
#34 (optia* or cobe* or terumo* or caridian* or gambro*):ti,ab,kw 204
#35 ((spectra or spectrar or spectratm or spectrartm) and exchang*):ti,ab,kw 12
#36 (manual* near/3 exchang*):ti,ab,kw 6
#37 {or #18-#36} 9423
#38 #17 and #37 Publication Year from 1993 to 2015 186
#39 #38 in Cochrane Reviews (Reviews and Protocols) 17

B.8: Source: Science Citation Index Expanded (SCI-EXPANDED) -- 1900-present / Conference Proceedings Citation Index- Science (CPCI-S) --1990-present

Interface / URL: Web of Science
Search date: 03/07/15
Retrieved records: 690
Search strategy:

Indexes=SCI-EXPANDED, CPCI-S Timespan=All years

36 690 (#35) AND LANGUAGE: (English) Timespan=1993-2015

35 821 #32 not #33 Refined by: [excluding] DOCUMENT TYPES: (EDITORIAL MATERIAL)

34 831 #32 not #33

33 2,423,214 TI=("rat" or "rats" or "rodent" or "rodents" or "mouse" or "mice" or "murine" or "hamster" or "hamsters" or "gerbil" or "gerbils" or "animal" or "animals" or "dogs" or "dog" or "canine" or "pig" or "pigs" or "piglet" or "piglets" or "cats" or "bovine" or "cow" or "cows" or "cattle" or "sheep" or "ewe" or "ewes" or "horse" or "horses" or "equine" or "ovine" or "porcine" or "monkey" or "monkeys" or "primate" or "primates" or "rhesus macaque" or "rhesus macaques" or "rabbit" or "rabbits") NOT TS=human*

32 837 #14 and #31

31 48,766 #30 OR #29 OR #28 OR #27 OR #26 OR #25 OR #24 OR #23 OR #22 OR #21 OR #20 OR #19 OR #18 OR #17 OR #16 OR #15

30 90 TS=(manual* near/3 exchang*)

29 26,255 TS=(("spectra" or "spectrar" or "spectratm" or "spectrartm") and (exchang* or transfusion*))

28 3,550 TS=(optia* or cobe* or terumo* or caridian* or gambro*)

27 645 TS=("blood cell*" near/3 (separator* or "separation" or "separating"))

26 881 TS=((automat* or "auto") near/3 exchang*)

25 7,745 TS=("apheresis" or "cytapheresis" or "cytopheresis" or "pheresis")

24 1,181 TS=(("chronic" or exsanguinatio* or "substitution" or "total" or "replacement") near/1 transfusion*)

23 1,275 TS=("EBT" or "EBTs")

22 5,657 TS=(exchang* near/3 (transfusion* or "blood"))

21 222 TS=("erythrocytapheresis")

20 7 TS=(erythroexchange*)

19 9 TS=("ARCET" or "RCET")

18 1,094 TS=("RBCX" or "RBCE" or "RCX" or "RCE")

17 797 TS=((erythrocyte* or normocyte*) near/3 exchang*)

16 157 TS=(("RBC" or "RBCs" or "RC" or "RCs") near/3 exchang*)

15 772 TS=(("red blood cell" or "red blood cells" or "red cell" or "red cells") near/3 exchang*)

14 44,583 #13 OR #12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1

13 3 TS=(meniscocyt*)

12 163 TS=(drepanocyt* or microdrepanocyt*)

11 1,074 TS=("sickling")

10 20 TS=("HBSD" or "HB-SD")

9 130 TS=("hemoglobin SD" or "haemoglobin SD" or "SD disease*")

8 477 TS=("HBSC" or "HB-SC")

7 388 TS=("hemoglobin SC" or "haemoglobin SC" or "SC disease*")

6 8,605 TS=("sickle" near/3 (anemia* or "hemoglobin" or anaemia* or "haemoglobin"))

5 1,329 TS=(("hemoglobin" or "haemoglobin") near/3 ("thalassemia" or "thalassaemia"))

4 8,096 TS=("HBS" or "HB-S" or "HBSS" or "HB-SS")

3 1,590 TS=("hemoglobin S" or "hemoglobin SS" or "haemoglobin S" or "haemoglobin SS" or "SS disease*")

2 14,302 TS=("SCA" or "SCD")

1 23,428 TS=("sickle cell*")

B.9: Source: PubMed

Interface / URL: http://www.ncbi.nlm.nih.gov/pubmed
Search date: 03/07/15
Retrieved records: 87
Search strategy:

#78 Search (#76 NOT #77) 87
#77 Search medline[sb] 22182655
#76 Search (#71 NOT (#72 OR #73)) Filters: Publication date from 1993/01/01 to 2016/12/31; English 814
#75 Search (#71 NOT (#72 OR #73)) Filters: English 1123

#74 Search (#71 NOT (#72 OR #73)) 1213
#73 Search (news[pt] OR comment[pt] OR editorial[pt]) 1041519
#72 Search animals[mh] NOT humans[mh:noexp] 4017663
#71 Search (#30 AND #70) 1267

#70 Search (#31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69) 54974

#69 Search (manual*[ot] AND exchang*[ot]) 4

#68 Search (manual*[tiab] AND exchang*[tiab]) 664

#67 Search ((spectra[ot] OR spectrar[ot] OR spectratm[ot] OR spectrartm[ot]) AND (exchang*[ot] OR transfusion*[ot])) 4

#66 Search ((spectra[tiab] OR spectrar[tiab] OR spectratm[tiab] OR spectrartm[tiab]) AND (exchang*[tiab] OR transfusion*[tiab])) 5747

#65 Search (optia*[ot] OR cobe*[ot] OR terumo*[ot] OR caridian*[ot] OR gambro*[ot]) 30

#64 Search (optia*[tiab] OR cobe*[tiab] OR terumo*[tiab] OR caridian*[tiab] OR gambro*[tiab]) 1618

#63 Search (blood cell*[ot] AND (separator*[ot] OR separation[ot] OR separating[ot])) 3

#62 Search (blood cell*[tiab] AND (separator*[tiab] OR separation[tiab] OR separating[tiab])) 2134

#61 Search ((automat*[ot] OR auto[ot]) AND exchang*[ot]) 20

#60 Search ((automat*[tiab] OR auto[tiab]) AND exchang*[tiab]) 2998

#59 Search (apheresis[ot] OR cytapheresis[ot] OR cytopheresis[ot] OR pheresis[ot]) 197

#58 Search (apheresis[tiab] OR cytapheresis[tiab] OR cytopheresis[tiab] OR pheresis[tiab]) 5844

#57 Search "cytapheresis" [mh:noexp] 302

#56 Search exsanguinatio*[ot] AND transfusion*[ot] 1

#55 Search exsanguinatio*[tiab] AND transfusion*[tiab] 169

#54 Search ((substitution[ot] OR total[ot] OR replacement[ot]) AND transfusion*[ot]) 62

#53 Search chronic transfusion*[ot] 3

#52 Search (chronic transfusion*[tiab] OR substitution transfusion* [tiab] OR total transfusion* [tiab] OR replacement transfusion* [tiab]) 493

#51 Search (EBT[ot] OR EBTs[ot]) 8

#50 Search (EBT[tiab] OR EBTs[tiab]) 801

#49 Search (exchang*[ot] AND (transfusion*[ot] OR blood[ot])) 837

#48 Search (exchang*[tiab] AND (transfusion*[tiab] OR blood[tiab])) 22913

#47 Search erythrocytapheresis[ot] 10

#46 Search erythrocytapheresis[tiab] 153

#45 Search erythroexchange*[ot] 0

#44 Search erythroexchange*[tiab] 6

#43 Search (ARCET[ot] OR RCET[ot]) 0

#42 Search (ARCET[tiab] OR RCET[tiab]) 9

#41 Search (RBCX[ot] OR RBCE[ot] OR RCX[ot] OR RCE[ot]) 6

#40 Search (RBCX[tiab] OR RBCE[tiab] OR RCX[tiab] OR RCE[tiab]) 407

#39 Search ((erythrocyte*[ot] OR normocyte*[ot]) AND exchang*[ot]) 102
#38 Search ((erythrocyte*[tiab] OR normocyte*[tiab]) AND exchang*[tiab]) 3311
#37 Search ((RBC[ot] OR RBCs[ot] OR RC[ot] OR RCs[ot]) AND exchang*[ot]) 5
#36 Search ((RBC[tiab] OR RBCs[tiab] OR RC[tiab] OR RCs[tiab]) AND exchang*[tiab]) 797
#35 Search ((red blood cell[ot] OR red blood cells[ot] OR red cell[ot] OR red cells[ot]) AND exchang*[ot]) 17
#34 Search ((red blood cell[tiab] OR red blood cells[tiab] OR red cell[tiab] OR red cells[tiab]) AND exchang*[tiab]) 2916
#33 Search "blood component removal" [mh:noexp] 3798
#32 Search "Erythrocyte Transfusion" [mh:noexp] 6640
#31 Search "Exchange Transfusion, Whole Blood" [mh:noexp] 4129
#30 Search (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29) 44548
#29 Search meniscocyt*[ot] 0
#28 Search meniscocyt*[tiab] 3
#27 Search (drepanocyt*[ot] OR microdrepanocyt*[ot]) 19
#26 Search (drepanocyt*[tiab] OR microdrepanocyt*[tiab]) 354
#25 Search sickling[ot] 9
#24 Search sickling[tiab] 1282
#23 Search (HBSD[ot] OR HB-SD[ot]) 3
#22 Search (HBSD[tiab] OR HB-SD[tiab]) 27
#21 Search hemoglobin SD[ot] OR (haemoglobin[ot] AND SD[ot]) OR (SD[ot] AND disease*[ot]) 111
#20 Search (hemoglobin SD[tiab] OR haemoglobin SD[tiab] OR SD disease*[tiab]) 123
#19 Search (HBSC[ot] OR HB-SC[ot]) 6
#18 Search (HBSC[tiab] OR HB-SC[tiab]) 638
#17 Search (hemoglobin SC[ot] OR haemoglobin SC[ot] OR SC disease*[ot]) 11
#16 Search (hemoglobin SC[tiab] OR haemoglobin SC[tiab] OR SC disease*[tiab]) 384
#15 Search "Hemoglobin SC Disease" [mh:noexp] 558
#14 Search (sickle[ot] AND (anemia*[ot] OR hemoglobin[ot] OR anaemia*[ot] OR haemoglobin[ot])) 1537
#13 Search (sickle[tiab] AND (anemia*[tiab] OR hemoglobin[tiab] OR anaemia*[tiab] OR haemoglobin[tiab])) 10158
#12 Search ((hemoglobin[ot] OR haemoglobin[ot]) AND (thalassemia[ot] OR thalassaemia[ot])) 162
#11 Search ((hemoglobin[tiab] OR haemoglobin[tiab]) AND (thalassemia[tiab] OR thalassaemia[tiab])) 4615
#10 Search "Hemoglobin, Sickle" [mh:noexp] 2718
#9 Search (HBS[ot] OR HB-S[ot] OR HBSS[ot] OR HB-SS[ot]) 159
#8 Search (HBS[tiab] OR HB-S[tiab] OR HBSS[tiab] OR HB-SS[tiab]) 10795

#7 Search (hemoglobin S[ot] OR hemoglobin SS[ot] OR haemoglobin S[ot] OR haemoglobin SS[ot] OR SS disease*[ot]) 17
#6 Search (hemoglobin S[tiab] OR hemoglobin SS[tiab] OR haemoglobin S[tiab] OR haemoglobin SS[tiab] OR SS disease*[tiab]) 1811
#5 Search (SCA[ot] OR SCD[ot]) 189
#4 Search (SCA[tiab] OR SCD[tiab]) 11462
#3 Search sickle cell*[ot] 2070
#2 Search sickle cell*[tiab] 18694
#1 Search "anemia, sickle cell" [mh:noexp] 17101

B.10: Source: Econlit 1886 to June 2015

Interface / URL: OvidSP
Search date: 03/07/15
Retrieved records: 10
Search strategy:

1 sickle cell$1.af. (6)
2 (h?emoglobin S or h?emoglobin SS or SS disease$1).af. (0)
3 (h?emoglobin adj3 thalass?emia).af. (0)
4 (sickle adj3 (an?emia$ or h?emoglobin)).af. (1)
5 (h?emoglobin SC or SC disease$1).af. (0)
6 (h?emoglobin SD or SD disease$1).af. (0)
7 sickling.af. (0)
8 (drepanocyt$ or microdrepanocyt$).af. (0)
9 meniscocyt$.af. (0)
10 or/1-9 (7)
11 (SCA or SCD or HBS or HB-S or HBSS or HB-SS or HBSC or HB-SC or HBSD or HB-SD).af. (106)
12 ((exchang$ or RBCX or RBCE or RCX or RCE or ARCET or RCET or erythroexchange$1 or erythrocytapheresis or EBT or EBTs or transfusion$1 or apheresis or cytapheresis or cytopheresis or pheresis or blood cell$1 or optia$ or cobe$ or terumo$ or caridian$ or gambro$) not (balassa and samuelson)).af. (71401)
13 11 and 12 (3)
14 10 or 13 (10)
15 limit 14 to (yr="1993 -Current" and english) (10)

B.11: Source: HEED: Health Economic Evaluations Database

Interface / URL: EBSCOHOST
Search date: 03/07/15
Retrieved records: 9
Search strategy:

S27 S14 AND S24 Limiters - Published Date: 19930101-20161231; Language: English 9
S26 S14 AND S24 9

S24 S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 870
S23 TX(optia* OR cobe* OR terumo* OR caridian* OR gambro*) 8
S22 TX("blood cell*" N3 (separator* OR separation OR separating)) 1
S21 TX(apheresis OR cytapheresis OR cytopheresis OR pheresis) 33
S20 TX(EBT OR EBTs) 1
S19 TX(erythrocytapheresis) 3
S18 TX(erythroexchange*) 0
S17 TX(ARCET OR RCET) 0
S16 TX(RBCX OR RBCE OR RCX OR RCE) 0
S15 TX(exchang* OR transfusion*) 848
S14 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 97
S13 TX(meniscocyt*) 0
S12 TX(drepanocyt* OR microdrepanocyt*) 0
S11 TX(sickling) 1
S10 TX(HBSD OR "HB-SD") 0
S9 TX("hemoglobin SD" OR "haemoglobin SD" OR "SD disease*") 1
S8 TX(HBSC OR "HB-SC") 0
S7 TX("hemoglobin SC" OR "haemoglobin SC" OR "SC disease*") 2
S6 TX(sickle N3 (anemia* OR hemoglobin OR anaemia* OR haemoglobin)) 39
S5 TX((hemoglobin OR haemoglobin) N3 (thalassemia OR thalassaemia)) 1
S4 TX(HBS OR "HB-S" OR HBSS OR "HB-SS") 14
S3 TX("hemoglobin S" OR "hemoglobin SS" OR "haemoglobin S" OR "haemoglobin SS" OR "SS disease*") 0
S2 TX(SCA OR SCD) 23
S1 TX("sickle cell*") 65

B.12: Source: CEA Registry

Interface / URL: https://research.tufts-nemc.org/cear4/
Search date: 03/07/15
Retrieved records: 0
Search strategy:

Basic search used at: https://research.tufts-nemc.org/cear4/SearchingtheCEARegistry/SearchtheCEARegistry.aspx ('search for articles' selected)

Following searches run individually. Results viewed online to check for SCD context and relevance. Irrelevant records were excluded.

sickle = 0 records returned
scd = 0 (8 records returned, 0 relevant)
hemoglobin s = 0 records returned
haemoglobin s = 0 records returned

hemoglobin ss = 0 records returned
haemoglobin ss = 0 records returned
ss disease = 0 records returned
ss diseases = 0 records returned
hbs = 0 (6 records returned, 0 relevant)
hb-s = 0 records returned
hbss = 0 records returned
hb-ss = 0 records returned
thalassemia = (4 records returned, 0 relevant)
thalassaemia = (5 records returned, 0 relevant)
hemoglobin sc = 0 records returned
haemoglobin sc = 0 records returned
sc disease = (3 records returned, 0 relevant)
sc diseases = 0 records returned
hbsc = 0 records returned
hb-sc = 0 records returned
hemoglobin sd = 0 records returned
haemoglobin sd = 0 records returned
sd disease = 0 records returned
sd diseases = 0 records returned
hbsd = 0 records returned
hb-sd = 0 records returned
sickling = 0 records returned
drepanocytemia = 0 records returned
drepanocytaemia = 0 records returned
drepanocytic = 0 records returned
drepanocytosis = 0 records returned
microdrepanocytemia = 0 records returned
microdrepanocytaemia = 0 records returned
microdrepanocytic = 0 records returned
microdrepanocytosis = 0 records returned
meniscocytosis = 0 records returned

Note: ‘sca’ not searched on; term does not perform efficiently in the interface.

B.13: Source: ClinicalTrials.gov

Interface / URL: https://clinicaltrials.gov/ct2/home
Search date: 03/07/15
Retrieved records: 80
Search strategy:

The following searches were carried out. All results (125) were downloaded into an EndNote library with de-duplication settings at default. 45 records were removed as within-set duplicates, 80 records were retrieved.

1. (sickle OR "hemoglobin s" OR "haemoglobin s" OR "hemoglobin ss" OR "haemoglobin ss" OR "ss disease" OR "ss diseases" OR "hemoglobin sc" OR "haemoglobin sc" OR "sc disease" OR "sc diseases" OR "hemoglobin sd" OR "haemoglobin sd" OR "sd disease" OR "sd diseases" OR sickling OR drepanocytemia OR drepanocytaemia OR drepanocytic OR drepanocytosis OR microdrepanocytemia OR microdrepanocytaemia OR microdrepanocytic OR microdrepanocytosis OR meniscocytosis) AND (exchange OR exchanges OR RBCX OR RBCE OR RCX OR RCE OR ARCET OR RCET OR erythroexchange OR erythroexchanges OR erythrocytapheresis OR EBT OR EBTs OR apheresis OR cytapheresis OR cytopheresis OR pheresis OR separator OR separators OR separation OR separating OR optia OR cobe OR terumo OR caridian OR gambro OR optiar OR cober OR terumor OR caridianr OR gambror OR optiatm OR cobetm OR terumotm OR caridiantm OR gambrotm OR optiartm OR cobertm OR terumortm OR caridianrtm OR gambrortm OR spectra OR spectrar OR spectratm OR spectrartm) = 28 results

2. (sickle OR "hemoglobin s" OR "haemoglobin s" OR "hemoglobin ss" OR "haemoglobin ss" OR "ss disease" OR "ss diseases" OR "hemoglobin sc" OR "haemoglobin sc" OR "sc disease" OR "sc diseases" OR "hemoglobin sd" OR "haemoglobin sd" OR "sd disease" OR "sd diseases" OR sickling OR drepanocytemia OR drepanocytaemia OR drepanocytic OR drepanocytosis OR microdrepanocytemia OR microdrepanocytaemia OR microdrepanocytic OR microdrepanocytosis OR meniscocytosis) AND (chronic OR exsanguination OR substitution OR total OR replacement) AND (transfusion OR transfusions) = 45 results

3. (hemoglobin OR haemoglobin) AND (thalassemia OR thalassaemia) AND (exchange OR exchanges OR RBCX OR RBCE OR RCX OR RCE OR ARCET OR RCET OR erythroexchange OR erythroexchanges OR erythrocytapheresis OR EBT OR EBTs OR apheresis OR cytapheresis OR cytopheresis OR pheresis OR separator OR separators OR separation OR separating OR optia OR cobe OR terumo OR caridian OR gambro OR optiar OR cober OR terumor OR caridianr OR gambror OR optiatm OR cobetm OR terumotm OR caridiantm OR gambrotm OR optiartm OR cobertm OR terumortm OR caridianrtm OR gambrortm OR spectra OR spectrar OR spectratm OR spectrartm) = 4 results

4. (hemoglobin OR haemoglobin) AND (thalassemia OR thalassaemia) AND (chronic OR exsanguination OR substitution OR total OR replacement) AND (transfusion OR transfusions) = 16 results

5. (SCA OR SCD OR hbs OR "hb-s" OR hbss OR "hb-ss" OR hbsc OR "hb-sc" OR hbsd OR "hb-sd") AND (blood OR "red cell" or "red cells" OR RBC or RBCs or RC or RCs OR erythrocyte or normocyte OR erythrocytes or normocytes OR transfusion OR transfusions OR spectra or spectrar or spectratm or spectrartm) AND (exchange OR exchanges) = 18 results

6. (SCA OR SCD OR hbs OR "hb-s" OR hbss OR "hb-ss" OR hbsc OR "hb-sc" OR hbsd OR "hb-sd") AND (RBCX OR RBCE OR RCX OR RCE OR ARCET OR RCET OR erythroexchange OR erythroexchanges OR erythrocytapheresis OR EBT OR EBTs OR apheresis OR cytapheresis OR cytopheresis OR pheresis OR "cell separator" OR "cell separators" OR "cell separation" OR optia OR cobe OR terumo OR caridian OR gambro OR optiar OR cober OR terumor OR caridianr OR gambror OR optiatm OR cobetm OR terumotm OR caridiantm OR gambrotm OR optiartm OR cobertm OR terumortm OR caridianrtm OR gambrortm) = 14 results

7. (SCA OR SCD OR hbs OR "hb-s" OR hbss OR "hb-ss" OR hbsc OR "hb-sc" OR hbsd OR "hb-sd") AND (spectra OR spectrar OR spectratm OR spectrartm) AND (transfusion OR transfusions) = 0 results

B.14: Source: WHO International Clinical Trials Registry Platform

Interface / URL: http://apps.who.int/trialsearch/Default.aspx
Search date: 03/07/15
Retrieved records: 37
Search strategy:

sickle AND exchang* OR sickle AND transfusion* OR sickle AND RBCX OR sickle AND RBCE OR sickle AND RCX OR sickle AND RCE OR sickle AND ARCET OR sickle AND RCET OR sickle AND erythroexchange* OR sickle AND erythrocytapheresis OR sickle AND EBT OR sickle AND EBTs OR sickle AND apheresis OR sickle AND cytapheresis OR sickle AND cytopheresis OR sickle AND pheresis OR sickle AND separat* OR sickle AND optia* OR sickle AND cobe* OR sickle AND terumo* OR sickle AND caridian* OR sickle AND gambro* OR sickle AND spectra OR sickle AND spectrar OR sickle AND spectratm OR sickle AND spectrartm = 37 (47 records for 37 trials)

B.15: Source: ISRCTN registry

Interface / URL: http://www.isrctn.com/
Search date: 03/07/15
Retrieved records: 3
Search strategy:

Advanced interface used.

Following terms entered into the ‘Conditions’ field search box and searched on separately. All returned results assessed online for relevance by information specialist.

Sickle = 3 (21 results returned; excluded as irrelevant)
SCA = 0
SCD = (2 results returned; excluded as irrelevant)

Hemoglobin = 0 (1 result returned; excluded as irrelevant)
haemoglobin = 0 (1 result returned; excluded as irrelevant)
SS disease = 0
SS diseases = 0
HBS = 0
HB-S = 0
HBSS = 0 (1 result returned; excluded as irrelevant)
HB-SS = 0
SC disease = 0
SC diseases = 0
HBSC = 0
HB-SC = 0
SD disease = 0
SD diseases = 0
HBSD = 0
HB-SD = 0
drepanocytemia = 0
drepanocytaemia = 0
drepanocytic = 0
drepanocytosis = 0
microdrepanocytemia = 0
microdrepanocytaemia = 0
microdrepanocytic = 0
microdrepanocytosis = 0
meniscocytosis = 0

Note: ‘sickling’ not searched on; returns same results as a search on ‘sickle’

B.16: Source: British Society of Haematology website

Interface/URL: http://www.b-s-h.org.uk/
Search date: 02/07/2015
Retrieved records: 0
Search strategy:

The following search was carried out using the homepage search box:

sickle OR sca OR scd OR hemoglobin OR haemoglobin OR HBS

Results were screened / selected by type of document and by reference to the following intervention concepts, searched using CTRL F: exchange, transfusion, RBCX, RBCE, RCX, RCE, erythrocytapheresis, apheresis, cytapheresis, cytopheresis, pheresis, Optia, Cobe, Terumo, Spectra.

8 results were returned, 0 selected

B.17: Source: Royal College of Pathologists website
Interface/URL: http://www.rcpath.org/
Search date: 02/07/2015
Retrieved records: 0
Search strategy:

The following search was carried out using the homepage search box:

sickle OR sca OR scd OR hemoglobin OR haemoglobin OR HBS

Results were screened / selected by type of document and by reference to the following intervention concepts, searched using CTRL F: exchange, transfusion, RBCX, RBCE, RCX, RCE, erythrocytapheresis, apheresis, cytapheresis, cytopheresis, pheresis, Optia, Cobe, Terumo, Spectra.

15 results were returned, 0 selected

B.18: Source: Rare Disease UK website
Interface/URL: http://www.raredisease.org.uk/
Search date: 02/07/2015
Retrieved records: 0
Search strategy:

No search functionality available via website. Site searched using Google advanced search.

Following search carried out:

sickle OR sca OR scd OR hemoglobin OR haemoglobin OR HBS
site:http://www.raredisease.org.uk/

Results were screened / selected by type of document and by reference to the following intervention concepts, searched using CTRL F: exchange, transfusion, RBCX, RBCE, RCX, RCE, erythrocytapheresis, apheresis, cytapheresis, cytopheresis, pheresis, Optia, Cobe, Terumo, Spectra.

16 results were returned, 0 selected

B.19: Source: UK Forum on Haemoglobin Disorders website
Interface/URL: http://www.haemoglobin.org.uk/

Search date: 02/07/2015
Retrieved records: 6
Search strategy:

No search functionality available via website. Site searched using Google advanced search.

Following search carried out:

sickle OR sca OR scd OR hemoglobin OR haemoglobin OR HBS site:http://www.haemoglobin.org.uk/

Results were screened / selected by type of document and by reference to the following intervention concepts, searched using CTRL F: exchange, transfusion, RBCX, RBCE, RCX, RCE, erythrocytapheresis, apheresis, cytapheresis, cytopheresis, pheresis, Optia, Cobe, Terumo, Spectra.

50 results were returned, 6 selected

B.20: Source: Action for Sick Children website
Interface/URL: http://www.actionforsickchildren.org.uk/
Search date: 02/07/2015
Retrieved records: 0
Search strategy:

No search functionality available via website. Site searched using Google advanced search.

Following search carried out:

sickle OR sca OR scd OR hemoglobin OR haemoglobin OR HBS site:http://www.actionforsickchildren.org.uk/

Results were screened / selected by type of document and by reference to the following intervention concepts, searched using CTRL F: exchange, transfusion, RBCX, RBCE, RCX, RCE, erythrocytapheresis, apheresis, cytapheresis, cytopheresis, pheresis, Optia, Cobe, Terumo, Spectra.

0 results were returned

B.21: Source: African Caribbean Leukaemia Trust website

Interface/URL: http://www.aclt.org/index.php/home/
Search date: 02/07/2015
Retrieved records: 0
Search strategy:

The following search was carried out using the homepage search box:

sickle OR sca OR scd OR hemoglobin OR haemoglobin OR HBS

Results were screened / selected by type of document and by reference to the following intervention concepts, searched using CTRL F: exchange, transfusion, RBCX, RBCE, RCX, RCE, erythrocytapheresis, apheresis, cytapheresis, cytopheresis, pheresis, Optia, Cobe, Terumo, Spectra.

15 results were returned, 0 selected

B.22: Source: Bliss website
Interface/URL: http://www.bliss.org.uk/
Search date: 02/07/2015
Retrieved records: 0
Search strategy:

Individual searches on the following terms were carried out using the homepage search box.

sickle = 0 results
SCA = 86 returned, 0 selected
SCD = 0 results
hemoglobin = 0 results
haemoglobin = 2 returned, 0 selected
HBS = 0 results

Results were screened / selected by type of document and by reference to the following intervention concepts, searched using CTRL F: exchange, transfusion, RBCX, RBCE, RCX, RCE, erythrocytapheresis, apheresis, cytapheresis, cytopheresis, pheresis, Optia, Cobe, Terumo, Spectra.

B.23: Source: Different Strokes website
Interface/URL: http://www.differentstrokes.co.uk/
Search date: 02/07/2015
Retrieved records: 0

Search strategy:

Individual searches on the following terms were carried out using the homepage search box.

sickle = 0 results
SCA = 47 returned, 0 selected
SCD = 0 results
hemoglobin = 0 results
haemoglobin = 0 returned, 0 selected
HBS = 0 results

Results were screened / selected by type of document and by reference to the following intervention concepts, searched using CTRL F: exchange, transfusion, RBCX, RBCE, RCX, RCE, erythrocytapheresis, apheresis, cytapheresis, cytopheresis, pheresis, Optia, Cobe, Terumo, Spectra.

B.24: Source: Ethnic Health Foundation website
Interface/URL: http://www.ehfl.org/
Search date: 02/07/2015
Retrieved records: 0
Search strategy:

No search functionality available via website. Site searched using Google advanced search.

Following search carried out:

sickle OR sca OR scd OR hemoglobin OR haemoglobin OR HBS site:http://www.ehfl.org/

Results were screened / selected by type of document and by reference to the following intervention concepts, searched using CTRL F: exchange, transfusion, RBCX, RBCE, RCX, RCE, erythrocytapheresis, apheresis, cytapheresis, cytopheresis, pheresis, Optia, Cobe, Terumo, Spectra.

3 results were returned, 0 selected

B.25: Source: National Childbirth Trust website
Interface/URL: http://www.nct.org.uk/
Search date: 02/07/2015

Retrieved records: 0
Search strategy:

The following search was carried out using the homepage search box:

sickle OR sca OR scd OR hemoglobin OR haemoglobin OR HBS

Results were screened / selected by type of document and by reference to the following intervention concepts, searched using CTRL F: exchange, transfusion, RBCX, RBCE, RCX, RCE, erythrocytapheresis, apheresis, cytapheresis, cytopheresis, pheresis, Optia, Cobe, Terumo, Spectra.

4 results were returned, 0 selected

B.26: Source: Sickle Cell and Young Stroke Survivors website
Interface/URL: http://www.scyss.org/
Search date: 02/07/2015
Retrieved records: 0
Search strategy:

No search functionality available via website. Site searched using Google advanced search.

Following search carried out:

sickle OR sca OR scd OR hemoglobin OR haemoglobin OR HBS
site:http://www.scyss.org/

Results were screened / selected by type of document and by reference to the following intervention concepts, searched using CTRL F: exchange, transfusion, RBCX, RBCE, RCX, RCE, erythrocytapheresis, apheresis, cytapheresis, cytopheresis, pheresis, Optia, Cobe, Terumo, Spectra.

39 results were returned, 0 selected

B.27: Source: Sickle Cell Society website
Interface/URL: http://sicklecellsociety.org/
Search date: 02/07/2015
Retrieved records: 1
Search strategy:

No search functionality available via website. Site searched using Google advanced search.

The following individual searches were carried out. Results were screened and potentially relevant results selected:

exchange site:http://sicklecellsociety.org/ = 3 returned, 1 selected
RBCX site:http://sicklecellsociety.org/ = 0 results
RBCE site:http://sicklecellsociety.org/ = 0 results
RCX site:http://sicklecellsociety.org/ = 0 results
RCE site:http://sicklecellsociety.org/ = 0 results
Erythrocytapheresis site:http://sicklecellsociety.org/ = 0 results
Apheresi site:http://sicklecellsociety.org/ = 0 results
Cytopheresis site:http://sicklecellsociety.org/ = 0 results
Pheresis site:http://sicklecellsociety.org/ = 0 results
Optia site:http://sicklecellsociety.org/ = 0 results
Cobe site:http://sicklecellsociety.org/ = 0 results
Terumo site:http://sicklecellsociety.org/ = 0 results
Spectra site:http://sicklecellsociety.org/ = 0 results

B.28: Source: Specialised Healthcare Alliance website
Interface/URL: http://www.shca.info/
Search date: 02/07/2015
Retrieved records: 0
Search strategy:
No search functionality available via website. Site searched using Google advanced search.

Following search carried out:

sickle OR sca OR scd OR hemoglobin OR haemoglobin OR HBS site:http://www.shca.info/

Results were screened / selected by type of document and by reference to the following intervention concepts, searched using CTRL F: exchange, transfusion, RBCX, RBCE, RCX, RCE, erythrocytapheresis, apheresis, cytapheresis, cytopheresis, pheresis, Optia, Cobe, Terumo, Spectra.

10 results were returned, 0 selected

B.29: Source: Stroke Association website

Interface/URL: https://www.stroke.org.uk/
Search date: 02/07/2015
Retrieved records: 0
Search strategy:

Individual searches on the following terms were carried out using the homepage search box.

sickle = 8 returned, 0 selected
sca = 1 returned, 0 selected
scd = 0 results
hemoglobin = 0 results
haemoglobin = 1 returned, 0 selected
hbs = 0 results

Results were screened / selected by type of document and by reference to the following intervention concepts, searched using CTRL F: exchange, transfusion, RBCX, RBCE, RCX, RCE, erythrocytapheresis, apheresis, cytapheresis, cytopheresis, pheresis, Optia, Cobe, Terumo, Spectra.

B.30: Source: Together for Short Lives website
Interface/URL: http://www.togetherforshortlives.org.uk/
Search date: 02/07/2015
Retrieved records: 2
Search strategy:

Individual searches on the following terms were carried out using the homepage search box.

Sickle = 31 returned, 0 selected
SCA = 1 returned, 1 selected
SCD = 11 returned, 0 selected
Haemoglobin = 3 returned, 1 selected
Hemoglobin = 3 returned, 0 selected
HBS = 0 results

Results were screened / selected by type of document and by reference to the following intervention concepts, searched using CTRL F: exchange, transfusion, RBCX, RBCE, RCX, RCE, erythrocytapheresis, apheresis, cytapheresis, cytopheresis, pheresis, Optia, Cobe, Terumo, Spectra

B.31: Source: Tommy's website
Interface/URL: http://www.tommys.org/
Search date: 02/07/2015
Retrieved records: 0
Search strategy:

The following search was carried out using the homepage search box:

sickle OR sca OR scd OR hemoglobin OR haemoglobin OR HBS

Results were screened / selected by type of document and by reference to the following intervention concepts, searched using CTRL F: exchange, transfusion, RBCX, RBCE, RCX, RCE, erythrocytapheresis, apheresis, cytapheresis, cytopheresis, pheresis, Optia, Cobe, Terumo, Spectra.

8 results were returned, 0 selected

Conference searches

Records of abstracts presented at annual conferences (past 3 years) were sought for the following organisations; these meetings were specified in project discussions with NICE and the sponsor as the top three worldwide conferences where clinical evidence on Spectra Optia may have been presented.

- American Society for Apheresis (ASFA)
- American society of Haematology (ASH)
- British Society for Haematology (BSH)

The Embase list of covered conferences (http://www.elsevier.com/solutions/embase/coverage) was checked to see if any of the conferences of interest were already covered by the database search. The following conferences were included in Embase:

35th Annual Meeting of the American Society for Apheresis. 2014
34th Annual Meeting of the American Society for Apheresis. 2013
56th Annual Meeting of the American Society of Hematology, ASH 2014
55th Annual Meeting of the American Society of Hematology, ASH 2013

The 2015 ASH conference has not yet been held (due to be held December 5-8, 2015).

Hand-searches were therefore carried out for the following 4 conferences:

American Society for Apheresis 36th Annual Meeting, 2015
55th Annual Scientific Meeting of the British Society for Haematology, 2015
54th Annual Scientific Meeting of the British Society for Haematology, 2014
53rd Annual Scientific Meeting of the British Society for Haematology, 2013

B.32: Source: Abstracts From the American Society for Apheresis 36th Annual Meeting, 2015

Interface / URL: http://onlinelibrary.wiley.com/doi/10.1002/jca.v30.2/issuetoc
Search date: 07/07/15
Retrieved records: 14
Search strategy:

The Crtl F function was used to search across the following document:

Special Issue: Special Issue Abstracts From the American Society for Apheresis 36th Annual Meeting, May 6–9, 2015 San Antonio, Texas.
http://onlinelibrary.wiley.com/doi/10.1002/jca.v30.2/issuetoc

The following term was searched on:

sickle

Abstracts including the term were retrieved.

B.33: Source: Abstracts of the 55th Annual Scientific Meeting of the British Society for Haematology, 2015

Interface / URL: http://onlinelibrary.wiley.com/doi/10.1111/bjh.2015.169.issue-s1/issuetoc
Search date: 07/07/15
Retrieved records: 3
Search strategy:

The Crtl F function was used to search across the following document:

Special Issue: Abstracts of the 55th Annual Scientific Meeting of the British Society for Haematology, 20-22 April 2015, Edinburgh, UK.
http://onlinelibrary.wiley.com/doi/10.1111/bjh.2015.169.issue-s1/issuetoc

The following term was searched on:

sickle

Abstracts including this term were assessed for potential relevance to the interventions of interest. Abstracts judged to be not relevant were excluded.

Remaining abstracts (6) were checked against records identified by previous searches in the main project EndNote library. Only those abstracts not already identified by previous searches were retrieved for further assessment.

B.34: Source: Abstracts of the 54th Annual Scientific Meeting of the British Society for Haematology, 2014

Interface / URL: http://onlinelibrary.wiley.com/doi/10.1111/bjh.2014.165.issue-s1/issuetoc
Search date: 07/07/15
Retrieved records: 1
Search strategy:

The Crtl F function was used to search across the following document:

Special Issue: Abstracts of the 54th Annual Scientific Meeting of the British Society for Haematology, 28-30 April 2014, Birmingham, UK. http://onlinelibrary.wiley.com/doi/10.1111/bjh.2014.165.issue-s1/issuetoc

The following term was searched on:

sickle

Abstracts including this term were assessed for potential relevance to the interventions of interest. Abstracts judged to be not relevant were excluded.

Remaining abstracts (6) were checked against records identified by previous searches in the main project EndNote library. Only those abstracts not already identified by previous searches were retrieved for further assessment.

B.35: Source: Abstracts of the 53rd Annual Scientific Meeting of the British Society for Haematology, 2013

Interface / URL: http://onlinelibrary.wiley.com/doi/10.1111/bjh.2013.161.issue-s1/issuetoc
Search date: 07/07/15
Retrieved records: 2
Search strategy:

The Crtl F function was used to search across the following document:

Special Issue: Abstracts of the 53rd Annual Scientific Meeting of the British Society for Haematology, 15-17 April 2013, Liverpool, UK. http://onlinelibrary.wiley.com/doi/10.1111/bjh.2013.161.issue-s1/issuetoc

The following term was searched on:

sickle

Abstracts including this term were assessed for potential relevance to the interventions of interest. Abstracts judged to be not relevant were excluded.

Remaining abstracts (3) were checked against records identified by previous searches in the main project EndNote library. Only those abstracts not already identified by previous searches were retrieved for further assessment.