NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical Technologies Evaluation Programme

Sponsor submission of evidence:

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

Sponsor: Cedar Healthcare Technology Research Centre, on behalf of Terumo BCT

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Instructions for sponsors

This is the template for submission of evidence to the National Institute for Health and Care Excellence (NICE) as part of the Medical Technologies Evaluation Programme process for developing NICE medical technologies guidance. Use of the submission template is mandatory.

The purpose of the submission is for the sponsor to collate, analyse and present all relevant evidence that supports the case for adoption of the technology into the NHS in England, within the scope defined by NICE. Failure to comply with the submission template and instructions could mean that the NICE cannot issue recommendations on use of the technology.

The submission should be completed after reading the 'Medical Technologies Evaluation Programme Methods guide' and the 'Medical Technologies Evaluation Programme Process guide' available at www.nice.org.uk/mt. After submission to, and acceptance by, NICE, the submission will be critically appraised by an External Assessment Centre appointed by NICE.

Under exceptional circumstances, unpublished evidence is accepted under agreement of confidentiality. Such evidence includes 'commercial in confidence' information and data that are awaiting publication ('academic in confidence'). When data are 'commercial in confidence' or 'academic in confidence', it is the sponsor's responsibility to highlight such data clearly. For further information on disclosure of information, submitting cost models and equality issues, users should see section 11 of this document 'Related procedures for evidence submission'.

The submission should be concise and informative. The main body of the submission should not exceed 100 pages (excluding the pages covered by the template and appendices). The submission should be sent to NICE electronically in Word or a compatible format, not as a PDF file.

The submission must be a stand-alone document. Additional appendices may only be used for supplementary explanatory information that exceeds the level

of detail requested, but that is considered to be relevant to the case for adoption. Appendices will not normally be presented to the Medical Technologies Advisory Committee when developing its recommendations. Any additional appendices should be clearly referenced in the body of the submission. Appendices should not be used for core information that has been requested in the specification. For example, it is not acceptable to attach a key study as an appendix and to complete the economic evidence section with ‘see appendix X’.

All studies and data included in the submission must be referenced. Identify studies by the first author or trial ID, rather than by relying on numerical referencing alone (for example, ‘Trial 123/Jones et al.[126], rather than ‘one trial[126]’).Please use a recognised referencing style, such as Harvard or Vancouver.

The sponsor should provide a PDF copy of full journal articles or reports – in electronic or hard copy form – included in the submission, if the sponsor is either the copyright owner or has adequate copyright clearance to permit the intended use by NICE. This clearance must be wide enough to allow NICE to make further copies, store the article electronically for a limited period of time on a shared drive to be accessed by a limited number of staff. Additionally, any full article obtained and submitted in electronic format must be done so in a manner compliant with the relevant contractual terms of use permitting the sponsor electronic access to the article. If the sponsor does not have sufficient copyright clearance, they are asked to submit references or links only, or details of contacts for unpublished research. NICE will then itself obtain full copies of all relevant papers or reports, paying a copyright fee where necessary. For unpublished studies for which a manuscript is not available, provide a structured abstract about future journal publication. If a structured abstract is not available, the sponsor must provide a statement from the authors to verify the data provided.

If a submission is based on preliminary regulatory recommendations, the sponsor must advise NICE immediately of any variation between the preliminary and final approval.

Document key

Boxed text with a grey background provides specific and/or important guidance for that section. This should not be removed.

Information in highlighted black italic is to help the user complete the submission and may be deleted.

The user should enter text at the point marked 'Response' or in the tables as appropriate. 'Response' text may be deleted.

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Glossary of terms

Term	Definition
Acute chest syndrome (ACS)	A vaso-occlusive sickle cell crisis characterised by one or more symptoms of shortness of breath (dyspnoea), hypoxia, fever, pain, cough and sputum production.
Alloimmunisation	Transfusion recipients can develop antibodies to donor blood antigens. This risk is increased in SCD because donors are predominantly from a different ethnic background to the patient. When a patient develops alloimmunisation they are at risk of haemolytic reactions, which may occur several days post-procedure. Once developed it becomes more difficult for compatible blood to be identified for future transfusions.
Apheresis	The process of removing individual blood components from a patient or donor and returning the remaining components to them. Usually achieved by passing the blood through a centrifuge device that separates components according to their density. This can be used to harvest cells or plasma from donors as well as conduct depletion or exchange procedures for patients.
Extracorporeal blood volume (EBV)	The volume of blood in the patient circuit of the apheresis device.
Foetal haemoglobin (HbF)	Haemoglobin produced by the foetus in the last 7 months of development and usually persisting until around 6 months post-partum. This is not affected by the sickle cell gene and has a greater affinity for oxygen than adult haemoglobin (i.e. oxygen binds to it in preference).
Fraction of cells remaining (FCR)	The fraction of the patient's original red blood cells remaining post-procedure.
Haemoglobin (Hb)	The molecule in red blood cells that carries oxygen around the body.
Haemoglobin S % (HbS%)	The percentage of the patient's total haemoglobin that is sickled.
Haematocrit (Hct)	The percentage by volume of whole blood that is made up by RBCs.
Hydroxycarbamide (hydroxyurea)	A drug (normally used for chemotherapy) used to increase the production of foetal haemoglobin in adults with sickle cell disease as a long term treatment.
Depletion/exchange, or isovolemic haemodilution red blood cell exchange (IDH-RBCX)	A type of automated exchange protocol that includes a depletion phase followed by an exchange phase. As fewer red cells are present when donor cells are exchanged a reduced amount of donor cells are required to achieve the same post-procedure %HbS.
Priapism	Painful persistent erection. This is a complication of sickle cell disease in which the sickled red blood occlude the small vessels in the penis.
Red blood cell depletion	A quantity of the patient's red blood cells are removed and replaced by an equal volume of fluid (saline or albumin).

Term	Definition
Red blood cell exchange (RBCX)	Red blood cells are removed from the patient's blood and replaced with healthy donor cells. This reduces the proportion of HbS cells in the blood.
Sickle cell anaemia (SCA)	The most common type of sickle cell disease in which two copies of the sickle cell genes have been inherited (HbSS).
Sickle cell crisis	An acute episode of severe pain due to vaso-occlusion by sickled red blood cells. May last for days or months and require emergency hospital treatment.
Sickle cell disease (SCD)	A group of recessive genetic blood disorders in people who have inherited two copies of a mutated gene for haemoglobin. The sickle gene can be combined with another sickle gene (in which case the condition is referred to as HbSS), or one for a different mutation such as thalassaemia (HbSβ). When deoxygenated, an abnormality in the haemoglobin molecule causes the red blood cells to become rigid and deform into a sickle-like shape. These cannot flow normally through small blood vessels and they can cause blockages.
Sickle cell trait	A condition in which a person has inherited one copy of the sickle gene for haemoglobin. The condition is much milder than sickle cell disease as the patient can still produce around 50% of normal haemoglobin.
Splenic sequestration	The spleen has narrow vessels and its function is to remove old red blood cells and metabolise haemoglobin. It is therefore especially vulnerable to damage in sickle cell disease and is often infarcted before adulthood due to vaso-occlusion. This leaves the patient vulnerable to infection.
Top-up (simple) transfusion (TUT)	Donor red blood cells are infused intravenously, as per a normal blood transfusion. No venesection is performed. The total haematocrit is increased, but as the donor red cells 'dilute' the autologous red cells the proportion of sickled cells (HbS%) is reduced.

Section A – Decision problem

Section A describes the decision problem, the technology and its clinical context. There is also information about ongoing studies, regulatory information and equality issues.

Sponsors should submit section A before the full submission (for details on timelines, see the NICE document 'Guide to the Medical Technologies Evaluation Programme process', available from www.nice.org.uk/mt

1 Statement of the decision problem

The decision problem is specified in the final scope issued by NICE. The decision problem states the key parameters that should be addressed by the information in the evidence submission. All statements should be evidence based and directly relevant to the decision problem.

Table A1 Statement of the decision problem

	Scope issued by NICE	Variation from scope	Rationale for variation
Population	Sickle cell disease patients requiring a medium or long-term transfusion regime.	None	
Intervention	Spectra Optia apheresis device	Also included data from Cobe Spectra apheresis device	Devices are essentially equivalent. See section 2.1 and sponsor table 2.
Comparator(s)	Manual red blood cell exchange	Included: • Comparisons between Cobe Spectra system and Spectra Optia system • Simple or 'top-up' transfusions	• To demonstrate equivalence in clinical outcomes. • See below
Outcomes	Primary outcomes • Percentage of total haemoglobin that is HbS (HbS%), relative to target percentage (usually <30%) • Duration of exchange procedure • Frequency of treatment • Patient haematocrit (measure relative to prescribed target for therapy) • Iron overload and requirement for chelation therapy • Clinical outcomes including frequency of stroke, multi-organ failure, acute chest syndrome and pain crises	Alloimmunisation rates and donor exposure have been included where reported	Alloimmunisation is a known side effect of transfusion therapies and is considered to increase with the level of donor exposure. Automation increases the number of units of blood use during the exchange and therefore these are important safety considerations.

	• Quality of life • Length of hospital stay • Staff time and staff group/grade • Frequency of top-up transfusion required to treat sickle cell complications Secondary outcomes • Ease of venous access, bruising and haematoma • Device-related adverse events • Hospital admissions • Donor blood usage • BMI and growth in children		
Cost analysis	Comparator(s): Manual red blood cell exchange Costs will be considered from an NHS and personal social services perspective. The time horizon for the cost analysis will be sufficiently long to reflect any differences in costs and consequences between the technologies being compared. Sensitivity analysis will be undertaken to address uncertainties in the model parameters, which will include scenarios in which different numbers and combinations of devices are needed.	Included top-up transfusions	See below
Subgroups to be considered	• 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 • Children	Acute chest syndrome (ACS) is an acute crisis. Patients are often treated for this as an emergency and not as part of an ongoing transfusion regime. However, some patients receive chronic transfusions to prevent frequent crises such as ACS.	

Special considerations, including issues related to equality	Sickle cell disease can have a substantial and long-term adverse effect on the ability to carry out normal day-to-day activities, and as such many people with sickle cell disease will be considered to be disabled, a protected characteristic under the Equality Act, 2010. Some religious groups, for example Jehovah's Witnesses, are opposed to blood transfusions. Religion and belief is a protected characteristic under the Equality Act, 2010. The majority of people with sickle cell disease in the UK are of black African or Caribbean family origin. There is currently an inequity of access to the highest standards of care for sickle cell disease as treatments are only available in certain cities in the UK.		

Rationale for Amending the Decision Problem to Include Top-up Transfusions

The vast majority of transfusions for SCD are simple red cell transfusions, packed red cells administered intravenously. Simple or top-up transfusions are useful where added oxygen carrying capacity is needed. Unless accompanied by bleeding or rapid red cell destruction, both the haemoglobin concentration and the viscosity of the blood will increase. Unfortunately transfusion does not fully resolve the problems associated with SCD. Red cell exchange transfusion is an effective but underutilised therapy for both acute and chronic complications of SCD. Exchange prevents the removed sickled cells from participating in new vaso-occlusive events, reduces haemolytic complications, and provides added oxygen carrying capacity while decreasing the blood viscosity. Children receiving long term top-up transfusion are highly likely to develop iron overload and require chelation therapy, which is both expensive and has unpleasant side effects. Eventually these patients may be

transferred to a manual or automated service (where available) in order to manage their iron loading. We believe that if these patients were transferred to exchange therapy at an earlier stage then the risks associated with iron overloading and chelation therapy could be substantially reduced. There is supportive evidence that red blood exchange is superior to other transfusion regimes, top-up as well as manual. Therefore we believe the decision problem needs to be amended to reflect current practice in the UK.

2 Description of technology under assessment

2.1 Give the brand name, approved name and details of any different versions of the same device.

Spectra Optia® Apheresis System

Cobe® Spectra Apheresis System is previous device from the same manufacturer, Terumo BCT. The manufacture has also previously been known as Cobe BCT, Gambro BCT and Caridian BCT. The Cobe Spectra Apheresis System has been superseded by the Spectra Optia system and was also used to provide automated red blood cell exchange. Automated red blood cell exchange and depletion/exchange on the Cobe Spectra system was carried out by the operator manipulating pump flow rates according to a specific method. Initially these were implemented and shared by clinical users rather than by the manufacturer. Due to the popularity of the Cobe Spectra system being used in this way the Spectra Optia system was designed to provide automated red blood cell exchange (RBCX) and depletion/exchange by use of a built-in software protocol.

The differences between the Cobe Spectra system and Spectra Optia system partly relate to usability and partly to the technical function. The Spectra Optia system is smaller, more portable and has a graphical user interface and data storage. The disposable tubing set for RBCX is also used for plasma exchange procedures.

Both devices use a centrifugal system for separating blood components, but utilise different mechanisms to identify the components to remove. The Cobe

Spectra system used set complex algorithms and needed the operator to monitor the interface to identify the components; whereas the Spectra Optia system uses the automated interface management (AIM) system. The AIM system monitors the removal of blood components and alerts the operator. This allows the operator to focus on the patient, rather than monitoring the machine.

Table A2: RBCX protocol comparison of Cobe Spectra system and Spectra Optia system

Cobe Spectra system	Spectra Optia system
2 dedicated procedures: Exchange Depletion Can do depletion exchange, but is not a dedicated procedure.	3 dedicated procedures: Exchange Depletion Depletion/Exchange
Rinseback: Operator manually overrides rinseback	Rinseback: System defaults to NO rinseback for all procedures (can still be performed if needed)
Interface Control: Algorithm control and the operator monitors interface position	Interface Control: Algorithm control AIM system- monitors and alerts operator
Data Entry : Exchange: system prompts for required data. Depletion; operator must remember data needed to perform depletion	Data Entry Exchange, Depletion, Depletion/Exchange: system prompt operator for required data for all 3 procedures
Blood Prime: Is considered part of the procedure	Custom prime Defined custom prime sequence, is not considered part of the procedure
AC Management: AC infusion rate not displayed (requires complex calculation to determine)	AC Management: AC infusion rate displayed on the main run screen and can be directly adjusted
FCR Calculation: Operator/Physician must calculate	FCR calculation System will calculate based on pre laboratory data and targeted post

Summary of differences:

- 3 dedicated procedures on the Spectra Optia system give more flexibility to customise the procedure to the patient needs and procedural goals.
- Data entry reduces need to remember the information needed for procedures and how to enter information to reach procedural targets. Recommended ranges based on patient information are given. When procedural targets cannot be attained, the system will give recommendations for new targets.
- FCR Calculation eliminates need to manually calculate the target FCR
- Interface Control AIM allows the operator to spend more focused time on patient
- Custom prime allows for a defined custom prime sequence and is not considered part of the procedure. It is differentiated in the procedure summary screen
- Anticoagulant (AC) management eliminates the need for lengthy manual calculations and allows direct control of AC infusion rate to better manage citrate toxicity
- Rinse back difference between Cobe Spectra system and Spectra Optia system eliminates the potential to forget to override rinse back. Is considered for fluid balance for accurate fluid balance targeting.
- There is a smaller extracorporeal volume on the Spectra Optia system (185ml max) compared to the Cobe Spectra system (285ml) meaning fluid balance is easier to maintain. There is no need to manipulate the system on the Spectra Optia system to perform the desired procedure.

With respect to clinical outcomes and blood parameters in SCD, the Cobe Spectra system and Spectra Optia system are essentially equivalent devices for automated RBCX and depletion/exchange protocol. In the clinical evidence we have identified 3 studies that compared these devices for this indication. Procedure duration, pre and post procedure HbS and haematocrit, FCR and

adverse events were not different between the devices. In most cases RBC volumes used and blood volume processed were not different. Poullin et al (2014) found a small but statistically significant increase in the RBC volume used when measured in millilitres, but not when measured in units, when using Spectra Optia system. This is in opposition to the small and statistically non-significant decrease in number of blood units reported by Turhan et al (2013) and Perseghin et al (2013a). Turhan et al (2013) reported a small but statistically significant decrease in blood volume processed when measured in millilitres with the Spectra Optia system, but not when measured in units. Poullin et al. (2014) found no difference in blood volume processed.

We therefore conclude that results from studies on automated red blood cell exchange using the Cobe Spectra system should be included as evidence to support the claims made for the Spectra Optia system. Outcomes from the three studies referred to above will be included and considered as single arm studies.

2.2 What is the principal mechanism of action of the technology?

RBCX procedures replace a patient's own red blood cells with healthy donor cells, thus reducing the proportion of sickled cells in the bloodstream. An apheresis device forms part of an extracorporeal circuit, removing individual blood components from the patient and returning the remaining components to bloodstream. The Spectra Optia system and Cobe Spectra system devices both use a centrifugal action to separate the blood components by density, removing the red cells to a bag. In an exchange procedure an equal volume of packed red cells is transfused into the patient simultaneously. In a depletion procedure the removed cells are replaced with an equal volume of fluid (saline, plasma or albumin).

3 Clinical context

3.1 Provide a brief overview of the disease or condition for which the technology is being considered in the scope issued by NICE.

<u>The Condition</u>

SCD is a group of recessive genetic blood disorders in people who have inherited two copies of a mutated gene for haemoglobin. One copy of the sickle gene can be combined with another copy of the sickle gene (HbSS), but other variants exist such as sickle/thalassaemia beta (HbSβ). People with two copies of the sickle cell gene have sickle cell anaemia (SCA) – this is the most common variant of the disease.

When deoxygenated, the sickle abnormality in the haemoglobin molecule causes the red blood cells to become rigid and deform into a sickle-like shape. These cannot flow normally through small blood vessels and they can cause blockages. When this happens oxygen is not delivered to the tissue producing localised hypoxia and pain, and potentially tissue damage. Sickle red blood cells (RBCs) also have a much shorter lifespan than normal RBCs – 10-20 days instead of 90-120 days. If the body is unable to replace the RBCs quickly enough then the patient will become anaemic. Complications of SCD include impaired growth in children, stroke, acute chest syndrome, increased vulnerability to infection due to splenic sequestration, priapism , renal complications and multi-organ failure. Life expectancy is significantly reduced, with a median expectancy of around 45-55 years (NHS Sickle Cell and Thalassaemia Screening Programme, 2010).

Epidemiology

In England around 250,000 people are thought to have the sickle cell trait (NHS Choices, 2014) and around 6000-12000 people with SCD in the UK (Sickle Cell Society, 2014; NCEPOD, 2008). A national screening program was introduced in England between 2003-2006 and records an average positive screening rate of 1:2000 (Streetly et al, 2010). (Note that screening can be refused so this is not the same as 1 per 2000 live births). The sickle cell gene is most prevalent in people of African descent, and in people from the Mediterranean, Middle East, India, the Caribbean and South and Central America (Sickle Cell Society, 2008). Therefore local prevalence rates can vary widely according to demographics.

The National Haemoglobinopathy Registry (NHR) 2013-14 report indicates that 49 English NHS centres treated 7338 sickle cell patients, although data entry is not mandatory so this is likely to be a slight underestimate of the true population (NHR 2014). Prevalence rates are highest in London and the North West, Yorkshire and Humber and the West Midlands. The report indicates just over 600 patients were treated with transfusions of which 332 received regular transfusions. We assume that this number combines simple top-up transfusions and all exchange procedures (manual and automated), but again must be treated as an underestimate. Hospital Episode Online (HES) data for England indicates that the number of patients with a diagnostic code for sickle cells disease (ICD-10 D57.1) and a procedure code of red cell exchange (OPCS X32.6) indicates 1411 procedures for 313 patients in 2012-13. However, this data is for inpatients and we would expect many patients receiving top-up transfusions and exchange procedures to be treated as outpatients. HES outpatient data is less complete than inpatient data as 'main procedure' is not a mandated field. A national enquiry into deaths in sickle cell patients reports an average hospital admission rate for England of 28 per 100,000 for 0-18 year olds (NCEPOD, 2008).

Therapy

The first line of therapy, if lifestyle advice is inadequate, is hydroxycarbamide (hydroxyurea). This is a chemotherapy drug that increases the production of foetal haemoglobin. Normally foetal haemoglobin production stops around 6 months post-partum, but it can be resumed and this is not subject to the sickle mutation. However, it has side effects, is ineffective in some patients and contraindicated in patients planning to conceive or during pregnancy and breastfeeding.

Some patients with SCD receive simple top-up blood transfusions as a means to treat anaemia and/or increase the proportion of normal haemoglobin in their blood (HbA). This can be used as an emergency treatment for vaso-occlusive crises, or for short or long term prophylaxis. The resulting increase in the haematocrit can suppress the production of new red blood cells (erythropoiesis) and increases the total oxygen carrying capacity. However,

this will increase the blood viscosity (when >30%), which carries risks of complications, and also risks iron overload when continued as a chronic regime. Iron chelation therapy (e.g. Deferasirox) can be prescribed but this has significant gastrointestinal and other side effects and compliance can be poor.

Manual red blood cell exchange is an alternative to top-up transfusions in which some of the patient's blood is removed (venesection) before the donor blood is transfused. This has the advantage of decreasing the proportion of sickle red blood cells (HbS) without increasing the viscosity and reducing the probability of iron accumulation. However, the procedure is time consuming, requires considerable calculation and is labour intensive. If large volumes are required to be exchanged, several cycles of venesection and transfusion may be required. In this case the patient may need an inpatient stay of a couple of days to complete the procedure.

Automated red blood cell exchange is conducted using an apheresis device. It removes the patient's own red blood cells and replaces them with a combination of fluid and donor cells. The device works continuously and reduces the time for treatment and is less labour intensive than manual exchange. However, the equipment and consumable costs are high.

All transfusion therapies include a risk of the patient developing alloimmunisation antibodies. This is partly due to the donor and recipient populations being from different ethnic origins. The risk is thought to increase with the number of individual donors the patient's immune system is exposed to. This is referred to as donor exposure and is greater with automated exchange where a larger volume of donor blood is used.

Evidence basis for simple/top-up transfusion therapy

The vast majority of transfusions for SCD are top-up (simple) red blood cell transfusions (Smith-Whitely et al. 2012) which are packed red blood cells administered intravenously. Top-up transfusions are useful where additional oxygen carrying capacity is needed or if only a modest reduction in the proportion of HbS containing RBCs is required. However, the effectiveness of

top-up transfusion is limited by the need to avoid hypervolemia and/or hyperviscosity (Danielson 2002) caused by the transfusion of RBCs.

Rapid and excessive blood transfusion to haemoglobin levels of greater than 12 g/dL increases blood viscosity and can lead to stroke (Smith-Whitely et al. 2012; Ohene-Frempong et al. 1998; Russell et al. 1976).

In several landmark randomised controlled trials (RCT), chronic transfusion has been shown to prevent recurrent overt strokes (Ware et al. 2012) and first overt stroke (Adams et al. 1998) in children with sickle cell anaemia. However, due to the increase iron levels and need for iron chelation therapy, RBCX would be more beneficial to the patients. Iron chelation medication has unpleasant side effects and they are often not taken as prescribed (Adams and Brambilla, 2005), leading to complications of iron overload.

Acute chest syndrome (ACS) describes a new pulmonary infiltrate with respiratory findings such as cough, dyspnoea, or new onset hypoxia in a patient with SCD. ACS is the leading cause of death and the second most common cause of hospitalisation among patients with SCD. Because ACS is not the presenting diagnosis in up to half of cases of SCD (Emre et al. 1995) identifying risk factors for pre-emptive therapy with transfusion is desirable. A dramatic reduction in hospitalisation for ACS (and pain) was observed in children undergoing chronic transfusion for primary stroke prevention compared with the observed group (Miller et al. 2009). However, whereas chronic transfusion therapy reduces the incidence of ACS events among patients with recurrent ACS, it may not necessarily reduce the severity of episodes (Hankins et al. 2005).

Benefits of exchange transfusions over top-up transfusion

RBCX can isovolemically replace HbS-containing RBCs with normal RBCs, thus maintaining a constant blood volume throughout the procedure. In addition, the haematocrit (Hct) can be more accurately estimated with RBCX. If a rapid and dramatic reduction of the proportion of HbS-containing RBCs is indicated, RBCX transfusion is preferable (Danielson et al. 2002). As described previously, an additional complication of transfusions is iron

overload, which can be decreased or avoided with an RBCX transfusion since the patient's RBCs are removed as they are replaced by allogeneic RBCs.

3.2 Give details of any relevant NICE or other national guidance or expert guidelines for the condition for which the technology is being used. Specify whether the guidance identifies specific subgroups and make any recommendations for their treatment. If available, these should be UK based guidelines.

In England sickle cell disease is part of the NHS national programme of care overseen by a clinical reference group (B08 – Haemoglobinopathies, previously National Definitions Set No 38). It is a specialised service that is commissioned on a regional basis. The National Haemoglobinopathies Project (June 2010 – July 2011) was hosted by the East Midlands Specialised Commissioning Group to provide guidance documents for commissioners. This included the designation standards for specialised haemoglobinopathies services published in July 2011 (East Midlands Specialised Commissioning Group, 2011), which forms the basis for the NHS standard contract for specialised services (NHS Commissioning Board, 2013)

Care for these conditions (primarily SCD and thalassaemia) should be provided by specialist haemoglobinopathy teams (SHTs) with planned care provided by local hospital teams (LHTs). Some formalised clinical networks also exist. The designation standards referred to above indicate that the prescription of long-term transfusion regimes should be conducted by SHTs, but the administration should be conducted locally to the patient. However, these documents do not refer to exchange transfusion explicitly. The Specialised Services National Definition Set No. 38 indicate that Specialised Haemoglobinopathy Services should provide exchange transfusions (manual or erythrocytapheresis) for severe complications of SCD as well as for chronic therapy (NHS Sickle Cell and Thalassaemia Screening Programme, 2010).

In 2010-11 there was a national programme of peer review visits to health services caring for children and young people with haemoglobin disorders. This was co-ordinated by the NHS West Midlands Quality Review Service

(WMQRS). This was followed by peer-review visits to adult services in 2012-13. (Reports from these are available on the WMQRS website http://www.wmqrs.nhs.uk/review-programmes). In 2014 a rolling programme of review visits for adult and paediatric services was initiated and new quality standards published. These standards identify that a specialist service should provide manual exchange on a 24/7 basis and that the clinical network should be able to provide erythrocytapheresis (West Midlands Quality Review Service, 2014). An example report from Sandwell and West Birmingham Hospitals NHS Trust from the 2012 review visit notes the absence of erythrocytapheresis and that patients had to travel to London or Bristol for this service (West Midlands Quality Review Service, 2013).

Related guidance includes:

Sickle cell acute painful episode: Management of an acute painful sickle cell episode in hospital. NICE guideline CG143 (2012).	This does not make any reference to transfusion or exchange therapies. Treatment of sickle cell crises is outside the scope of this evaluation.
Sickle Cell Disease in Childhood: standards and guidelines for clinical care. NHS Screening Programme (2010)	This refers to the need for exchange transfusion for certain severe SCD complication to be conducted preferentially at a specialist centre. There is a list of quality requirements for services providing regular transfusion therapy for SCD.
Standards for the Clinical Care of Children and Adults with Beta Thalassaemia in the UK. Sickle Cell Society (2008)	This includes standards on the organisation and commissioning of specialist services and the provision of transfusion therapies. The evidence for the use of different subgroups/ indications is discussed.
The management of sickle cell disease. National Heart, Lung and Blood Institute. (2002)	This includes the indications and conduct of exchange transfusions.

Handbook of Transfusion Medicine. United Kingdom Blood Services (2013).	Indications and complications of red cell transfusion and exchange in SCD.
Guideline on the clinical use of apheresis procedures for the treatment of patients and collection of cellular therapy products. British Committee for Standards in Haematology (Howell et al, 2015)	Includes standards and recommendations for the use of apheresis devices for red cell exchange in sickle cell disease.
Guideline on the management of acute chest syndrome in sickle cell disease. British Committee for Standards in Haematology (Howard et al, 2015)	Recommends chronic red cell exchange for prevention of recurrent ACS if medication is ineffective.

3.3 Describe the clinical pathway of care that includes the proposed use of the technology.

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

Due to the national neonatal screening programme most people with sickle cell should be identified early and have appropriate advice and access to specialist services. Regular attendance at a paediatric clinic with a local SCD healthcare team (LHT) should be available and with a specialist healthcare team (SHT) for annual review (NHS Sickle Cell and Thalassaemia Screening Programme, 2010). For adults, regular access to specialised clinics will depend on patient need. Guidelines indicate that regular transfusions are indicated to keep the HbS below 30% for primary and secondary stroke prevention as well as major elective surgery and painful crises in pregnancy (Sickle Cell Society, 2008). Exchange therapy is preferred where increased blood viscosity is a particular problem or if iron overload cannot be managed with chelation therapy.

Information from NHS hospitals indicates that, where both are available, manual exchange is most often used for emergency situations, as the apheresis service may only be used for planned procedures and away from the emergency and intensive care. Kuo et al (2015) lists the indications for regular exchange procedures used by two NHS London hospitals (one uses manual and the other uses Spectra Optia system). Patients on a regular treatment schedule will be booked into a specialist service in advance. For manual exchange or top-up transfusions these will be at intervals of around 4 weeks, and 7 weeks for automated exchange (Trompeter et al 2015a). If more than 3-4 units are required to be exchanged in order to reach the target of <30% HbS then the patient is likely to admitted as treatment will take longer than one day. The Nottingham Children's Hospital guideline for manual exchange recommends that the child be admitted to HDU or ITU before the procedure (Stokley, 2011). A survey of transfusion practice at 11 London

Hospitals indicated that adults were more likely to have an automated exchange and children a top-up transfusion, but that the hospital was the strongest determinant of treatment modality (Trompeter et al 2015a).

Patients will have multiple blood tests before and after the procedure, e.g. FBC, blood group, antibody screen and cross match, HbS%, urea and electrolytes (U&Es), liver function tests (LFTs), calcium, arterial blood gas, clotting studies. During manual exchange they will have additional tests during the procedure to determine how many cycles of exchange to conduct: FBC, HbS and electrolytes. Patients are generally monitored for about 30 minutes post-procedure, during which time they may have a saline drip for hydration.

3.4 Describe any issues relating to current clinical practice, including any uncertainty about best practice.

There is significant uncertainty regarding the indications for regular exchange rather than top-up transfusions. Local practice is likely to vary significantly with regard to availability, infrastructure and organisation. However, publically available NHS procedures for manual exchange appear to be very consistent.

3.5 Describe the new pathway of care incorporating the new technology that would exist if the technology was adopted by the NHS in England.

The pathway of care would not change significantly. The frequency of procedures for each patient will be lower and the procedure duration shorter. Indications will not change as a result of adopting the Spectra Optia system other than if the automated procedure creates capacity in an existing service and allows for additional patients to be treated. Local practice would determine whether the device would also be available for emergency procedures.

3.6 Describe any changes to the way current services are organised or delivered as a result of introducing the technology.

Although the Spectra Optia system requires additional training it can be used by a haematology nurse of band 5 or higher. It could be available in the same hospitals that currently use manual or top-up transfusions as chronic therapy. There are 57 NHS hospitals that currently have Spectra Optia system on-site. However of these, only 27 use it for automated red blood cell exchange and most of those carry out very few procedures. The device is a multipurpose apheresis machine that will be used for other procedures not related to sickle cell disease. Automated RBCX is provided according to local practice: for example at Central Middlesex this is available 9-5 whereas at Hammersmith Hospital it is available 24/7 (North West London Haemoglobinopathy Clinical Network, 2014). Both tertiary centres use Spectra Optia system.

Although the Optia is smaller and more portable than the Cobe Spectra system it is likely that automated exchange procedures will be organised around a single location as part of a specialist sickle cell or haematology service. Due to the shorter procedure times more patients on regular prophylactic therapy could be treated as outpatients or day case rather than requiring a hospital admission. However, the Spectra Optia system can only treat one patient at a time whereas the number of simultaneous manual exchanges is limited by staff availability. At centres which have a mature automated RBCX service (such as Guy's and St Thomas' Hospital) one nurse can monitor 2 Spectra Optia systems and therefore 2 patients simultaneously.

3.7 Describe any additional tests or investigations needed for selecting or monitoring patients, or particular administration requirements, associated with using this technology that are over and above usual clinical practice.

No additional tests are required. Due to the shorter procedure time and continuous operation, fewer intra-procedure blood tests (FBC, HbS and electrolytes.) may be required with the Spectra Optia system than for manual exchange, as the need to determine how many cycles of exchange to conduct are negated with the automated RBCX protocol. This is dependent on local standard operating procedures, so will vary from hospital to hospital.

3.8 Describe any additional facilities, technologies or infrastructure that need to be used alongside the technology under evaluation for the claimed benefits to be realised.

None required. The Spectra Optia system is a self-contained unit that requires no special facilities.

3.9 Describe any tests, investigations, interventions, facilities or technologies that would no longer be needed with using this technology.

No such items will be made redundant.

3.10 Describe how the NHS in England can disinvest from tests, investigations, interventions, facilities or technologies described in section 3.9 that would no longer be needed with using this technology.

NA

4 Regulatory information

4.1 Provide PDF copies of the following documents:

- instructions for use
- CE mark certificate or equivalent UK regulatory approval such as EC declaration of conformity
- quality systems (ISO 13485) certificate (if required).

Included are:

- Terumo BCT Declaration of Conformity (28 May 2014)
- BSI Quality assurance system certificate, certificate number CE00326 (28 January 2015)
- Spectra Optia Apheresis System RBCX Procedure Guide (March 2012)

4.2 Does the technology have CE mark for the indication(s) specified in the scope issued by NICE? If so, give the date that authorisation was received. If not, state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

Yes. The Spectra Optia system is a Class IIb medical device. The device originally received a CE mark in April 2007 for therapeutic plasma exchange. The red blood cell exchange protocol received the CE mark in November 2009. The certificates included in section 4.1 do not specifically mention the red blood cell procedure/protocol, but are generic to apheresis procedures.

4.3 Does the technology have regulatory approval outside the UK? If so, please provide details.

The Spectra Optia system achieved FDA 510(k) clearance in December 2013.

The device and the RBCX protocol are also cleared for use in the Middle East (Saudi Arabia, Bahrain, Oman Iran, Iraq, Israel, Jordon, Kuwait, Lebanon, Libya, Qatar, UAE, Syria), Ireland, Turkey, Germany, France, South Africa, Canada and Australia.

4.4 If the technology has not been launched in the UK provide the anticipated date of availability in the UK.

NA

4.5 If the technology has been launched in the UK provide information on the use in England.

There are 57 NHS hospital that currently have Spectra Optia system on-site. However of these, only 27 use it for automated red blood cell exchange and most of those carry out very few procedures. The device is a multipurpose apheresis machine that will be used for other procedures not related to sickle cell disease. Automated red cell exchange is primarily available in London and Manchester, and in Birmingham for paediatric patients only.

5 Ongoing studies

5.1 Provide details of all completed and ongoing studies on the technology from which additional evidence relevant to the decision problem is likely to be available in the next 12 months.

There are no ongoing studies known to the manufacturer or listed on trials websites (clinicaltrials.gov or ICTRP). The reference in section 6 of the Briefing Note does not relate to an ongoing study. Terumo BCT collates complaint data in an ongoing basis. There is a National Haemoglobinopathy Register (2014) and there may also be a European Haemoglobinopathy Register at Central Middlesex Hospital, but information on this is lacking.

5.2 If the technology is, or is planned to be, subject to any other form of assessment in the UK, please give details of the assessment, organisation and expected timescale.

None known.

6 Equality

NICE is committed to promoting equality of opportunity and eliminating unlawful discrimination on the grounds of age, disability, gender reassignment, race, religion or belief, sex, and sexual orientation, and to comply fully with legal obligations on equality and human rights.

Equality issues require special attention because of NICE's duties to have due regard to the need to eliminate unlawful discrimination, promote equality and foster good relations between people with a characteristic protected by the equalities legislation and others.

Any issues relating to equality that are relevant to the technology under assessment should be described. This section should identify issues described in the scope and also any equality issues not captured in the final scope.

Further details on equality may be found in section 11.3 of this document.

6.1.1 Describe any equality issues relating to the patient population and condition for which the technology is being used.

SCD can have a substantial and long-term adverse effect on the ability to carry out normal day-to-day activities, and as such many people with sickle cell disease will be considered to be disabled, a protected characteristic under the Equality Act, 2010.

Some religious groups, for example Jehovah's Witnesses, are opposed to blood transfusions. Religion and belief is a protected characteristic under the Equality Act, 2010.

The majority of people SCD in the UK are of black African, Middle Eastern or Caribbean family origin. Thus there is also geographical heterogeneity in patient distribution. The National Haemoglobinopathy Registry Report 2013-14 indicates that the greatest number of patients is in London, followed by the North West, Yorkshire and Humber, and East and West Midlands commissioning hubs. In comparison automated RBCX is primarily only

available in London, Manchester and Birmingham (only to paediatric patients). There is thus an inequity of access to the highest standards of care which means that some people have to travel long distances to receive treatment.

Pregnant women with SCD are at risk of additional complications which may affect both the mother and the foetus. Pregnancy and maternity is a protected characteristic under the Equality Act, 2010.

6.1.2 Describe any equality issues relating to the assessment of the technology that may require special attention.

People with sickle cell disease may be covered by the equalities legislation under the protected characteristic of disability. Use of this technology may have the potential to improve the quality of life for patients, therefore promoting equality.

6.1.3 How will the submission address these issues and any equality issues raised in the scope?

Where evidence relating to relevant subgroups (such as pregnant women) is available, this will be taken into consideration.

Section B – Clinical evidence

7 Published and unpublished clinical evidence

Section B requires sponsors to present published and unpublished clinical evidence for their technology.

Sponsors should read section 6 of the Medical Technologies Evaluation Programme methods guide on published and unpublished evidence, available from www.nice.org.uk/mt

All statements should be evidence-based and directly relevant to the scope. Reasons for deviating from the scope should be clearly stated and explained in table A1.

Sponsors are required to submit section B in advance of the full submission (for details on timelines, see the NICE document 'Guide to the Medical Technologies Evaluation Programme process', available from www.nice.org.uk/mt

7.1 Identification of studies

Published studies

7.1.1 Describe the strategies used to retrieve relevant clinical data from the published literature. Exact details of the search strategy used should be provided in section 10, appendix 1.

A structured literature search was devised. Initially we limited the search using the device names but this was found to be too restrictive and excluded relevant studies. The device names were combined (OR) with the terms 'manual' and 'automat$'. This was combined (AND) with terms for sickle cell disease and technology descriptors. The search was run in Medline, Medline in process, Embase, Scopus, Web of Science, Econlit, Pubmed and Cochrane databases.

When the search identified a study in a published conference proceeding the entire proceeding was subjected to a textword search to identify other abstracts related to red cell exchange. It became clear that conference abstracts published as journal issues were not all indexed in these databases. Due to the large number of appropriate conferences, the substantial number of papers already identified in our search and time constraints we have not conducted a systematic search of all conference proceedings.

The manufacturer also provided a small number of additional references that were not identified in our search strategy. In the light of these we reviewed our search strategy and decided to broaden it by removing the requirement for device names and replacing these terms with ‘exchang*’ OR ‘erythrocytapheres*’. This captured several additional references. This search was not integrated with the first, but was conducted separately and is listed separately in Appendix 1.

It was also decided to include simple/top-up transfusion as a comparator at this point. A further search strategy was devised to identify studies for this comparison, but it was found that all results had already been identified by the previous searches, so a separate search was not deemed necessary.

Unpublished studies

7.1.2 Describe the strategies used to retrieve relevant clinical data from unpublished sources.

No unpublished data is reported. None was identified by the manufacturer.

7.2 Study selection

Published studies

7.2.1 Complete table B1 to describe the inclusion and exclusion criteria used to select studies from the published literature. Suggested headings are listed in the table below. Other headings should be used if necessary.

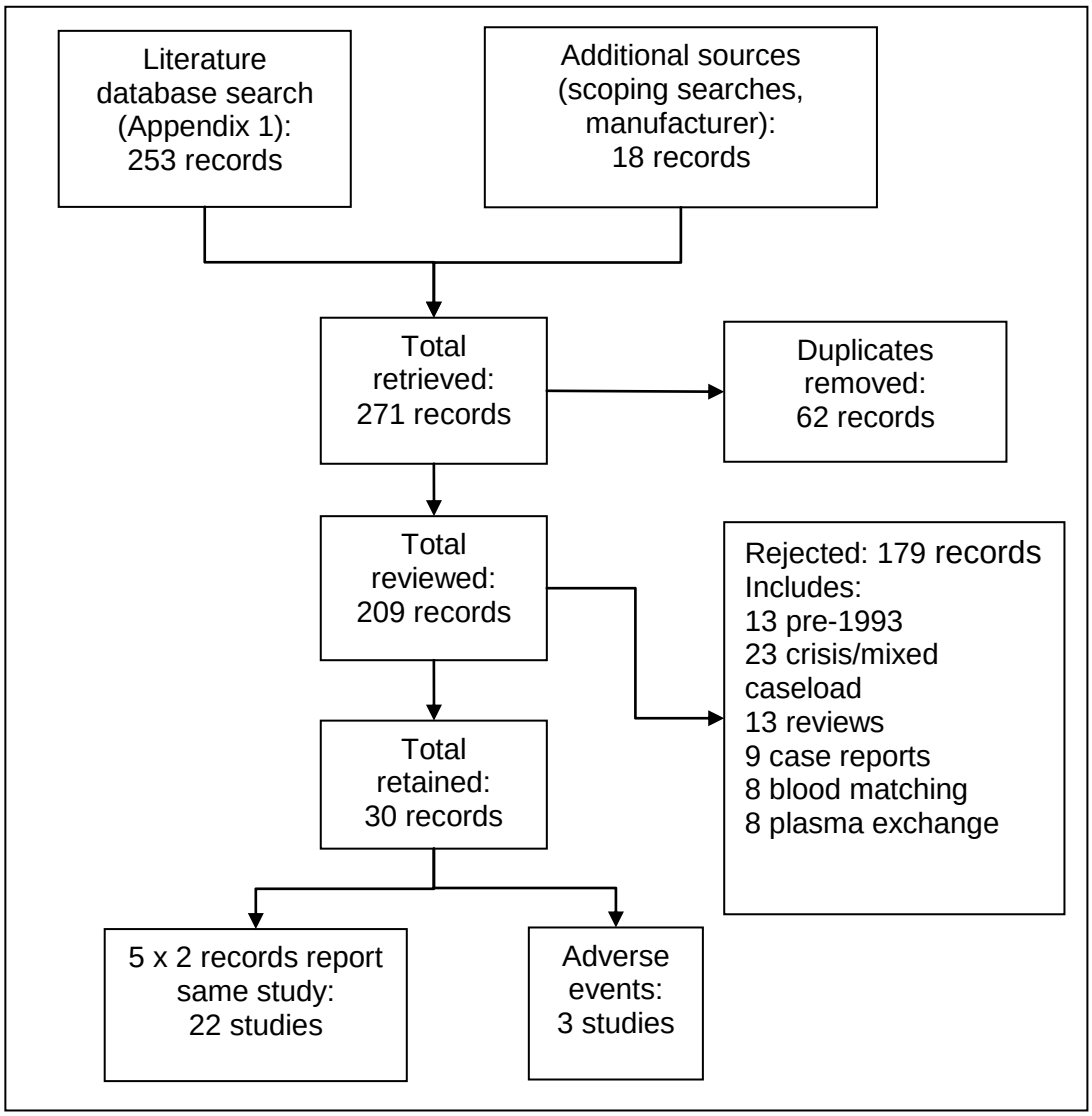
Table B1 Selection criteria used for published studies

Inclusion criteria	
Population	Sickle cell disease, including all subtypes
Interventions	Spectra Optia or Cobe Spectra systems described as automated red blood cell exchange procedures, including depletion/exchange and IHD-RBCX for chronic programmes of treatment
Outcomes	Any outcome listed in the scope plus alloimmunisation
Study design	Not restricted in search criteria
Language restrictions	English
Search dates	1993 – present day
Exclusion criteria	
Population	Patients being treated for sickle cell crisis emergencies, mixed populations where data could not be disaggregated. (Note that Perseghin et al, 2015 has been included to demonstrate equivalence of the RBCX procedure in Cobe Spectra system and Spectra Optia system.)
Interventions	Automated red blood cell exchange where the device could not be identified. One-off treatments, e.g. before surgery or during pregnancy.
Outcomes	Any additional outcomes with no immediate clinical reference
Study design	Case reports were excluded due to the large number of observational studies available
Language restrictions	Non-English language
Search dates	Pre-1993

7.2.2 Report the numbers of published studies included and excluded at each stage in an appropriate format.

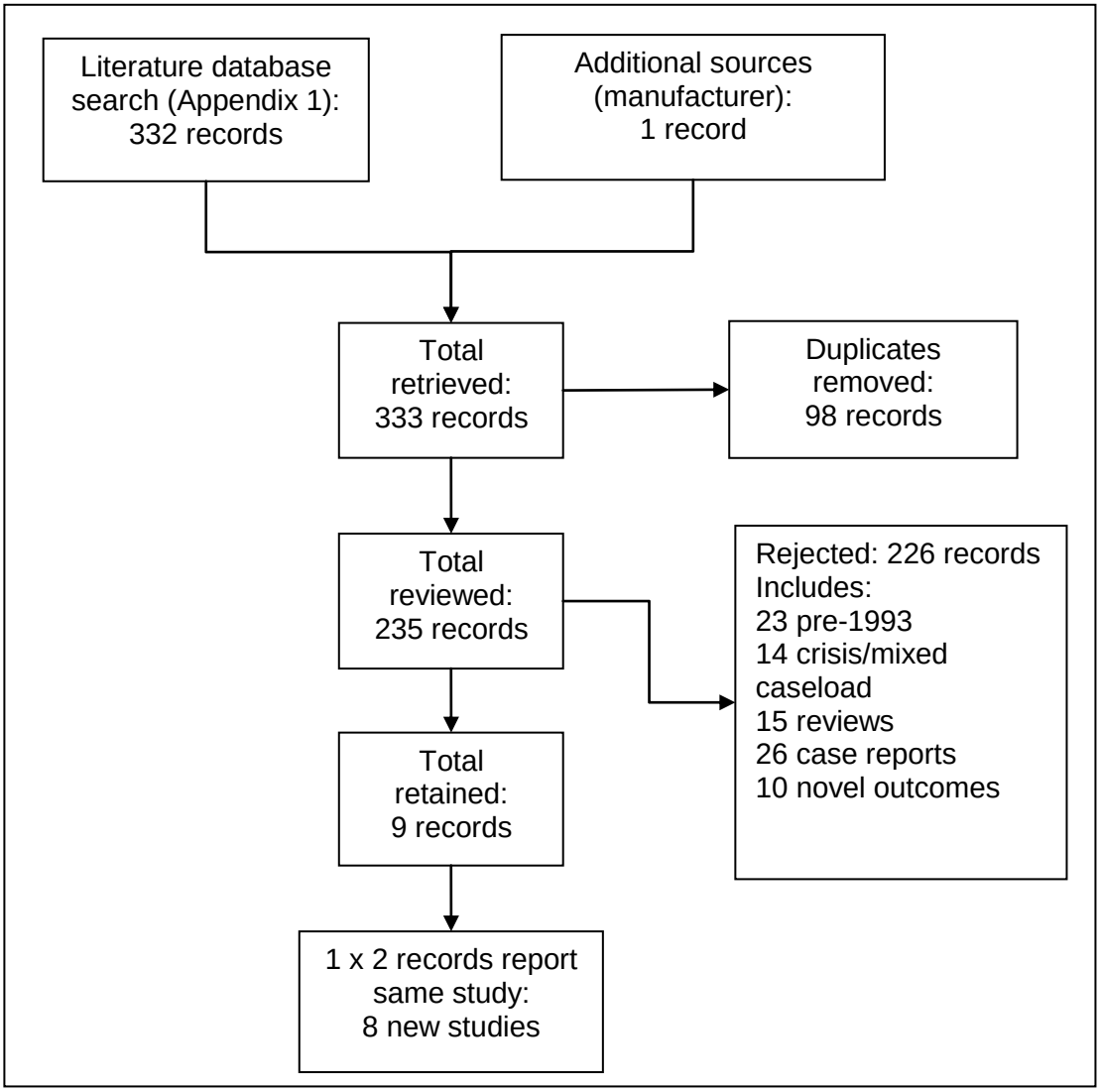
The first literature search strategy reported in Appendix 1 identified 253 references. An additional 18 references were identified by other means – provided by the manufacturer, from initial scoping searches or via Google searches for specific topics. Following deduplication this produced 209 unique records. Following sifting by title, abstract and full-text 30 records were identified as within the scope of the evaluation, excluding case reports. Of these, 5 were found to be reports of either the same study or with substantial overlap as another. Therefore 25 studies were included in the clinical evidence review from this search, of which 3 contain information solely relating to adverse events.

Figure 1: PRISMA diagram for first search strategy



The additional literature search strategy reported in Appendix 1 identified 332 references. An additional reference was provided by the manufacturer. Following deduplication this produced 235 unique records. Following sifting by title, abstract and full-text 9 records were identified as within the scope of the evaluation, excluding case reports. Of these, 1 was found to be a report of the same study as another. Therefore there were an additional 8 studies from this literature search and 33 studies in total included in the clinical evidence review, of which 3 contain information solely relating to adverse events.

Figure 2: PRISMA diagram for additional search



Unpublished studies

7.2.3 Complete table B2 to describe the inclusion and exclusion criteria used to select studies from the unpublished literature. Suggested headings are listed in the table below. Other headings should be used if necessary.

No unpublished studies were identified.

Table B2 Selection criteria used for unpublished studies

Inclusion criteria	
Population	
Interventions	
Outcomes	
Study design	
Language restrictions	
Search dates	
Exclusion criteria	
Population	
Interventions	
Outcomes	
Study design	
Language restrictions	
Search dates	

7.2.4 Report the numbers of unpublished studies included and excluded at each stage in an appropriate format.

NA

7.3 Complete list of relevant studies

The sponsor should provide a PDF copy of all studies included in the submission if the sponsor is either the copyright owner or has adequate copyright clearance to permit the intended use by NICE. If the sponsor does not have sufficient copyright clearance, they are asked to submit references or links only, or details of contacts for unpublished studies. For unpublished studies for which a manuscript is not available, provide a structured abstract about future journal publication. If a structured abstract is not available, the sponsor must provide a statement from the authors to verify the data provided.

7.3.1 Provide details of all published and unpublished studies identified using the selection criteria described in tables B1 and B2.

Table B3 List of relevant published studies (letters relate to the table numbers in the subsequent sections)

Primary study reference	Population	Intervention	Comparator
Manual vs. Automated RBCX			
a: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
b:Dedeken et al, 2014	Older children with SCD receiving chronic exchange, previously treated with manual exchange	RBCX (Spectra Optia)	Manual exchange
c:Duclos et al, 2013	Children with SCD treated by chronic RBCX	RBCX (Cobe)	Manual exchange
d:Fasano et al, 2015/Kaushal et al, 2013	Children with SCD on iron chelation and chronic transfusion (3-way comparison)	RBCX (Spectra Optia)	Manual exchange and TUT
e:Kuo et al 2015/Kuo et al, 2012a	Adults with SCD and >1 RBCX over 1 year	RBCX (Spectra Optia)	Manual exchange
f:Woods et al, 2014	Children and teens with SCD receiving regular RBCX for stroke prevention	RBCX (Spectra Optia)	Manual exchange
Manual only			
g:Cararra et al, 2010	Adults and children with SCD unresponsive to hydroxyurea	Manual	-
h:Webb et al, 2014	Adults with SCD	Manual	-
Optia single arm			
i:Baker et al, 2013	Paediatric patients with SCD	RBCX (Spectra Optia)	-
j:Kuo et al, 2012b	Adults with SCD	depl-RBCX (Spectra Optia)	RBCX (Spectra Optia)
k:Quirolo et al, 2015/Quirolo et al, 2014	Teens and adults with SCD	depl-RBCX (Spectra Optia)	RBCX (Spectra Optia)
l:Sturgeon et al, 2009	Adults with SCD	RBCX (Spectra Optia)	No transfusion
m:Todd et al, 2015	Adults with SCD	RBCX (Spectra Optia)	-
n:Trompeter et al, 2015	Teens and adults with SCD receiving regular RBCX	depl-RBCX (Spectra Optia)	RBCX (Spectra Optia)
Cobe Spectra system /Spectra Optia system single arm			
o:Asma et al, 2014	Pregnant women with SCD	RBCX (both)	No transfusion
Cobe Spectra system single arm			

Primary study reference	Population	Intervention	Comparator
p:Bavle et al 2012/Bavle et al 2014	Children with SCD receiving RBCX for >1 year	RBCX (Cobe)	-
q:Billard et al, 2013	Children with SCD and poor venous access	RBCX (Cobe)	-
r:Kalff et al, 2010	Adults with SCD	RBCX (Cobe)	-
s:Ma et al, 2005	Teens and adults with SCD receiving chronic exchange for >12 months	IHD-RBCX (Cobe)	RBCX (Cobe)
t:Masera et al, 2007	Children with SCD at high risk for vaso-occlusive complications	RBCX (Cobe)	-
u:Sarode et al, 2011 / Myers et al, 2005	Adults with SCA, stable with history of thrombotic stroke	IHD-RBCX (Cobe)	RBCX (Cobe)
v:Shrestha et al, 2015	Adults with SCD on scheduled RBCX	RBCX (Cobe)	-
w:Willis et al, 2011	Young adults with SCD having monthly RBCX	RBCX (Cobe)	-
Spectra Optia system versus Cobe Spectra system			
x:Perseghin et al, 2013/Perseghin et al 2015	High risk adults and children with SCD receiving RBCX for prophylactic or emergency treatment.	RBCX (Spectra Optia)	RBCX (Cobe)
y:Poullin et al, 2014	Adults with SCD receiving chronic auto RBCX	Depl-RBCX (Spectra Optia)	IHD-RBCX (Cobe)
z:Turhan et al, 2013	Patients with SCD	RBCX (Spectra Optia)	RBCX (Cobe)
Auto RBCX versus top-up transfusion (TUT)			
aa:Adams et al, 1996	Children and teens with SCD	RBCX (Cobe)	TUT
ab:Fasano et al, 2015/Kaushal et al, 2013	Children with SCD on iron chelation and chronic transfusion (3-way comparison)	RBCX (Spectra Optia)	Manual exchange and TUT
ac:Hilliard et al, 1998	Teens and adults with SCD and a history of stroke converted from simple transfusion to auto RBCX	RBCX (Cobe)	TUT
ad:Singer et al, 1999	Children with SCD	RBCX (Cobe)	TUT

depl/RBCX – depletion/exchange procedure; RBCX – red blood cell exchange; IHD-RBCX – isovolemic haemodilution red blood cell exchange; TUT – top-up-transfusion

Table B4 List of relevant unpublished studies

NA

7.3.2 State the rationale behind excluding any of the published studies listed in tables B3 and B4.

None of the studies have been excluded from the evidence synthesis.

7.4 Summary of methodology of relevant studies

7.4.1 Describe the study design and methodology for each of the published and unpublished studies using tables B5 and B6 as appropriate. A separate table should be completed for each study.

Table B5 Summary of methodology for randomised controlled trials - NA

Tables B6a-f Summary of methodology for observational studies: manual versus automated RBCX studies

Study name	**a: Cabibbo et al, 2005**
Objective	To evaluate chronic manual and automatic RBCX in SCD
Location	Italy
Design	Unclear – we assume a retrospective observational study
Duration of study	Jan 1999 – Dec 2004
Patient population	Adults and children with SCD
Sample size	n = 20
Inclusion criteria	Patients with SCD at high risk for recurrent complications who had been hospitalised more than twice per year
Exclusion criteria	No additional criteria reported
Intervention(s) (n =) and comparator(s) (n =)	206 procedures in 13 patients (auto) 188 procedures in 7 patients (manual) 60/206 automated procedures carried out using Cobe Spectra system
Baseline differences	Patients receiving manual exchange had either poor compliance or difficulties with venous access
How were participants followed-up. Duration of follow-up, participants lost to follow-up	Not reported. We have assumed this is a retrospective review. Study duration is 6 years. Complications were noted “over an average of 6 years”.
Statistical tests	Not conducted
Outcomes	Procedure duration, number of RBC units, alloimmunisation rates, iron overload.

Study name	**b: Dedeken et al, 2014**
Objective	To assess the safety and efficacy of automated

	apheresis
Location	Belgium
Design	Retrospective review, observational case-crossover
Duration of study	Auto: Jan 2012 - June 2014 Manual: 6 months prior to this period
Patient population	Older children with SCD on a chronic transfusion programme treated using automated apheresis (RBCX) and previously treated with manual exchange (ME).
Sample size	n=10 patients, number of procedures not stated (n=181 used to report adverse events)
Inclusion criteria	Patients on ME were eligible to switch to RBCX if sufficient venous access (without central venous line) and weight ≥ 30kg.
Exclusion criteria	Not reported
Intervention(s) (n =) and comparator(s) (n =)	n=10 Intrapatient comparison. 181 procedures - unclear whether this was a total or referred to one of the subgroups.
Baseline differences	Median age, weight and height were all significantly higher ($p<0.0001$) in the RBCX group. Median age when RBCX was introduced was 11.8 years with median 1.9 years (range 0.5-4.4years) duration of ME.
How were participants followed-up. Duration of follow-up, participants lost to follow-up	Not reported.
Statistical tests	Friedman test was used to compare treatment across years and Dunn's Multiple Comparison Test to compare each year of treatment among them.
Primary outcomes	HbS, procedure duration, procedure interval, ferritin level, donor blood usage, adverse events

Study name	**c: Duclos et al, 2013**
Objective	Compare automated erythrocytapheresis with manual exchanges
Location	Two centres in France
Design	Retrospective cohort comparison, matched by age and weight.
Duration of study	2002 and 2008 for automated. Not reported for manual.
Patient population	Children undergoing chronic transfusion for SCD
Sample size	n = 10
Inclusion criteria	Not reported. Five patients treated using RBCX (1 centre) were selected and matched to 5 patients treated using ME (other centre) on age and weight.
Exclusion criteria	No additional criteria

Intervention(s) (n =) and comparator(s) (n =)	RBCX: 60 procedures in 5 patients ME: 124 procedures in 5 patients *Subgroup analyses: exchanges performed <40 days after the previous* *RBCX: 15 procedures* *ME: 109 procedures*
Baseline differences	RBCX patients were treated at one site (Clermont-Ferrand), the ME group at another site (Marseille). No other baseline differences are reported. The groups were reported as being matched by age and weight.
How were participants followed-up. Duration of follow-up, participants lost to follow-up	Only immediate post-procedure data are reported. Data is assumed to be routine clinical data analysed retrospectively. Duration of treatment or follow-up is not reported.
Statistical tests	Student t-test or Mann Whitney *U* test
Primary outcomes	Procedure duration, pre-procedure haematocrit, pre-procedure HbS, procedure interval, blood volume transfused, adverse events, acute SCD complications

Study name	**d: Fasano et al, 2015 / Kaushal et al, 2013***
Objective	Compare the effect of three transfusion modalities in SCD patients on iron overload
Location	Washington, USA
Design	Retrospective review of medical records. Comparison of 3 arms – RBCX, partial ME and simple transfusion.
Duration of study	Fasano: 44 months. Kaushal: 18 months
Patient population	Children with SCD on iron chelation and chronic transfusion.
Sample size	Fasano: n=36 Kaushal: n=25
Inclusion criteria	>6 months of haematologic data available
Exclusion criteria	No additional criteria
Intervention(s) (n =) and comparator(s) (n =)	Fasano: RBCX: n =10 ME: n = 6 (simple n = 20) Kaushal: RBCX: n = 5 ME: n = 6 (simple n = 14)
Baseline differences	Not reported
How were participants followed-up. Duration of follow-up, participants lost to follow-up	Not reported
Statistical tests	Random effects model and Kruskal Wallis test

Primary outcomes	HbS, ferritin, alloimmunisation rates

Study name	**e: Kuo et al 2012a / Kuo et al, 2015**
Objective	Quality assurance audit. Compared ME with RBCX for achievement of haematological targets, complications, blood usage and clinical outcome.
Location	Two centres in London: Bart's (manual) and Guy's and St. Thomas (RBCX).
Design	Retrospective observational comparative cohort study
Duration of study	May 2011 – Apr 2012
Patient population	Adult patients with SCD receiving regular red blood cell exchange
Sample size	n=51, number of procedures=401
Inclusion criteria	No additional criteria
Exclusion criteria	No additional criteria
Intervention(s) (n =) and comparator(s) (n =)	RCBX: n=30, number of procedures=199 ME: n=21, number of procedures=202
Baseline differences	The authors report no significant difference in baseline characteristics between the two groups. All of the RBCX group were treated at one site (Guy's and St. Thomas). The ME group were treated at another site (Bart's Health NHS Trust). Median age (range): RBCX: 31 yrs (19-66) vs. ME: 23 yrs (16-52), p=0.035
How were participants followed-up. Duration of follow-up, participants lost to follow-up	Not reported. The authors refer to a "relatively short follow-up period". It is presumed that patients were not followed up beyond the end of their (final) procedure.
Statistical tests	Baseline differences were analysed using a Mantel-Haenszel Odds Ratio and multivariate logistic regression. Chi-squared test was employed for all analyses with the exception of age and prescribed treatment interval, which were analysed by Mann-Whitney *U* test.
Primary outcomes	Achievement of targets, pre-procedure HbS, post-treatment haematocrit, procedure duration, prescribed treatment interval, procedure frequency, iron chelation, RBC usage, adverse events

Study name	**f: Woods et al, 2014**
Objective	To compare outcome between manual exchange (ME) and erythrocytapheresis (ECP)
Location	Washington, USA
Design	Retrospective cohort study

Duration of study	Jan 2008 - Dec 2012
Patient population	Children and teens with SCD receiving chronic transfusion therapy for stroke prevention
Sample size	n = 38
Inclusion criteria	Patients on transfusion therapy for ≥6 months
Exclusion criteria	Stroke following brain biopsy
Intervention(s) (n =) and comparator(s) (n =)	Overall: • Received exclusively ECP, n=5 • Received exclusively ME, n=17 • Received both modalities, n=16 • Ever received ECP, n=21 • Never received ECP, n=17 Most recent 12-months for each participant: • 13 received ECP • 25 received ME • 5 patients switched from ECP to ME due to stenosis precluding double-lumen port replacement.
Baseline differences	Younger patients receive ME and can receive ECP when they are large enough for a large bore double lumen port but may choose to remain on ME.
How were participants followed-up. Duration of follow-up, participants lost to follow-up	Subjects were censored at last date of follow-up or date of hematopoietic stem cell transplant.
Statistical tests	Categorical variables were compared with Fisher's exact test, and medians with the Mann-Whitney *U* test
Primary outcomes	Achievement of HbS, ferritin, total duration of transfusion therapy, catheter complications

Tables B6g-h Summary of methodology for observational studies: manual single arm studies

Study name	**g: Carrara et al, 2010**
Objective	To describe long-term follow-up of manual erythroexchange for chronic transfusion therapy in patients with SCD unresponsive to hydroxyurea.
Location	Italy
Design	Retrospective observational cohort study
Duration of study	Not clear. Data appear to be from the period between 1981 and 2010.
Patient population	Adults and children with SCD unresponsive to hydroxyurea
Sample size	n=7
Inclusion criteria	No additional criteria
Exclusion criteria	No additional criteria

Intervention(s) (n =)	922 procedures in 7 patients Median number of procedures was 133 (range 85-204)
Baseline differences	NA
How were participants followed-up. Duration of follow-up, participants lost to follow-up	There were a median of 22 years of follow-up data (range 14-29).
Statistical tests	Not conducted
Primary outcomes	Interval between each procedure, liver iron concentrations, HbS
Secondary outcomes	Acute complications of SCD, alloimmunisation, requirement for hospitalisation

Study name	**h: Webb et al. 2014**
Objective	Evaluate the ability to achieve paediatric hematologic goals in adults on manual RBCX for secondary stroke prophylaxis; determine the SCD-related admission rates
Location	USA
Design	Retrospective single arm cohort study
Duration of study	10 years, January 2004 to December 2013
Patient population	Adult with SCD on chronic RBCX for secondary stroke prophylaxis
Sample size	n=15
Inclusion criteria	≥1 years of RBCX procedures
Exclusion criteria	Not stated
Intervention(s) (n =) and comparator(s) (n =)	Manual RBCX
Baseline differences	7 male, 8 female Mean age 30.7 years at start (range 21.2 – 39.3)
How were participants followed-up. Duration of follow-up, participants lost to follow-up	Admissions data, laboratory data, and RBCX data from medical records. 89.6 patient years of observation
Statistical tests	Spearman's correlation testing in STATA version 12.0
Primary outcomes	Hb, haematocrit and HbS; procedure interval and frequency, incidence of stroke and hospital admissions

Table B6i-n Summary of methodology for observational studies: Spectra Optia system single arm studies

Study name	**i: Baker et al. 2013**
Objective	To report experience of using Spectra Optia
Location	Canada
Design	Retrospective single arm observational study
Duration of study	June 2010 to May 2012
Patient population	Paediatric patients with SCD (4-17 years)
Sample size	6 patients (54 procedures)
Inclusion criteria	Not stated
Exclusion criteria	Not stated
Intervention(s) (n =)	N = 6 (Spectra Optia)
Baseline differences	NA
How were participants followed-up. Duration of follow-up, participants lost to follow-up	Immediate post-procedure outcomes only.
Statistical tests	None
Primary outcomes	Pre/post procedure HbS (%), pre/post procedure haematocrit (L/L), blood volume processed, platelet loss
Secondary outcomes	Adverse events

Study name	**j: Kuo et al, 2012b**
Objective	Compare depletion/exchange RBCX to automated RBCX regarding donor exposure
Location	Toronto, Canada
Design	Retrospective observational before-and-after intrapatient comparative study
Duration of study	1 year before and 1 year after introduction of depletion/exchange (depl/RBCX) protocol Oct 2009 - Oct2011
Patient population	Adults with SCD
Sample size	7 patients, 135 procedures
Inclusion criteria	No additional criteria
Exclusion criteria	No additional criteria
Intervention(s) (n =) and comparator(s) (n =)	Comparison of laboratory and clinical outcomes for 1 year before and 1 year after the introduction of depletion/exchange RBCX using Spectra Optia. Number of depl/RBCX procedures=74 Number of RBCX procedures=61
Baseline differences	Not reported

How were participants followed-up. Duration of follow-up, participants lost to follow-up	Not reported
Statistical tests	Not stated
Primary outcomes	Pre-treatment HbS, post-treatment Hct, RBC volume, albumin volume, ferritin, iron chelation, procedure duration, adverse events

Study name	**k: Quirolo et al, 2015 / Quirolo et al, 2014**
Objective	Evaluate performance of Spectra Optia RBCX and depl/RBCX to achieve target FCR
Location	Five sites in US
Design	Prospective, multicentre, single-arm, open-label study (Protocols are combined for some outcomes and reported separately for others)
Duration of study	Not reported
Patient population	Teens and adults with SCD requiring exchange procedures as part of a chronic programme or as a single procedure.
Sample size	n=72 (enrolled), n=60 (evaluated)
Inclusion criteria	• Minimum age 12 years • Sufficient venous access • Able to commit to the follow-up schedule Patients were evaluable if they provided consent and had endpoint data were available.
Exclusion criteria	Patients treated in the lead-in phase (n=12) were not included in the evaluable population, but were included in the safety analyses.
Intervention(s) (n =)	n=72 (enrolled), n=60 (evaluated). Patients treated with RBCX (n=50), or depl/RBCX procedure (n=22). (Only one procedure per patient evaluated.)
Baseline differences	Not reported, single arm. Demographics reported
How were participants followed-up. Duration of follow-up, participants lost to follow-up	Vital signs were monitored during the procedure and at 1 hour post-procedure. Subjects were assessed for adverse events within 18-24 hours post-procedure. Efficacy analyses were conducted on data from all evaluable patients (n=60). Twelve additional (lead-in) patients were included in the safety analyses (n=72).
Statistical tests	Statistical tests (other than descriptive statistics) are not reported, although p-values feature in some results.

Primary outcomes	Actual FCR compared to target FCR Calculation of the primary endpoint ratio was based on actual cell fraction remaining (FCRa) divided by predicted fraction of the subject's original red blood cells remaining at the end of the procedure (FCRp).
Secondary outcomes	Haematocrit, HbS, procedure duration, blood volume processed, RBC volume, adverse events

Study name	**l: Sturgeon et al, 2009**
Objective	Impact of RBCX on hospital admissions
Location	St Georges Hospital, London
Design	Retrospective observational intra-patient before-and-after study
Duration of study	September 1995 to January 2009
Patient population	Adults with SCD. Mean age 37.5 years (range 19-73)
Sample size	74 patients, 1578 procedures Hospital admissions data available for 67/74 (91%) of patients. Patients were split into 4 groups: A: Regular RBCX at least every 8 weeks, n= 25 B Regular RBCX with occasional short breaks, n = 11 C: 3 or fewer exchanges per year, n = 5 D: 4 or fewer exchanges in total, n = 26 14/26 in group D excluded due to no lack of admissions/exchanges: n = 53 analysed
Inclusion criteria	Not stated
Exclusion criteria	No exchanges or hospital admissions in last 4 years On iron chelation
Intervention(s) (n =) and comparator(s) (n =)	RBCX: n = 74 Comparator: same patients prior to exchange transfusion programme.
Baseline differences	Patients on RBCX would be older – mean time on RBCX was 2.9 years (range 0-13)
How were participants followed-up. Duration of follow-up, participants lost to follow-up	Retrospective analysis of routine clinical data. At least 4 years of admission data examined, mean time on RBCX was 2.9 years (range 0-13).
Statistical tests	p-values given, tests not reported
Primary outcomes	Hospital admissions, RBC volume, ferritin

Study name	**m: Todd et al, 2015**

Objective	Determine the risk of iron overload in patients receiving automated RBCX
Location	Homerton Hospital, London
Design	Retrospective observational study
Duration of study	Not reported
Patient population	Adults with SCD receiving chronic automated RBCX
Sample size	N = 50 N = 19 evaluated for liver iron
Inclusion criteria	Patients with serial liver MRIs for liver iron assessment
Exclusion criteria	No additional criteria
Intervention(s) (n =) and comparator(s) (n =)	~400 procedures in 50 patients (number not given, but states mean of 8 procedures per patient (range 1-22))
Baseline differences	NA
How were participants followed-up. Duration of follow-up, participants lost to follow-up	Patients with serial MRIs (3) were followed up for 36 months. Retrospective analysis of routine clinical data was used.
Statistical tests	Not used
Primary outcomes	Liver iron accumulation at 12/18/24/36 months
Secondary outcomes	Red blood cells used

Study name	**n: Trompeter et al, 2015b**
Objective	Not stated
Location	London, UK
Design	Review of cases
Duration of study	Unknown
Patient population	Teens and adults with SCD receiving regular RBCX
Sample size	70 patients
Inclusion criteria	Age 13-67, >50 Kg Hct >25%
Exclusion criteria	Not stated
Intervention(s) (n =) and comparator(s) (n =)	Patients have HCT temporarily reduced to a minimum of 21% (max 6% reduction)
Baseline differences	unknown
How were participants followed-up. Duration of follow-up, participants lost to follow-up	A year of data pre and post intervention
Statistical tests	Unknown
Primary outcomes	Acceptability and savings in blood volume used

Table B6o Summary of methodology for observational studies: Cobe Spectra system / Spectra Optia system combined single arm studies

Study name	**Asma et al 2015**
Objective	Evaluate outcomes in pregnancy in SCD patients having preventive automated RBCX
Location	Turkey (single centre)
Design	Retrospective cross-sectional study
Duration of study	Jan 2000 – Mar 2013
Patient population	Pregnant women with SCD
Sample size	N = 37
Inclusion criteria	No additional criteria
Exclusion criteria	No additional criteria
Intervention(s) (n =) and comparator(s) (n =)	N = 24 automated RBCX N = 13 no transfusion therapy
Baseline differences	Not reported
How were participants followed-up. Duration of follow-up, participants lost to follow-up	Data was extracted retrospectively from routine clinical records. Follow-up appears to include the duration of pregnancy and immediate post-partum outcomes only. Patients were followed up for possible complications until discharge from the hospital.
Statistical tests	Wilcoxon for pre-post measures. Fisher exact test for categorical variables between groups.
Primary outcomes	Maternal and foetal complications
Secondary outcomes	Pre and post-procedure haematocrit and HbS%, blood volume processed, red blood cells used, adverse events, alloimmunisation and transfusion infection.

Tables B6p-w Summary of methodology for observational studies: Cobe Spectra system single arm studies

Study name	**p: Bavle et al, 2014/ Bavle et al. 2012**
Objective	Determine whether automated RBCX improves the growth rate and alters the age of peak growth velocity of children with SCD
Location	Kentucky, USA
Design	Retrospective observational comparative study. Data from SCD children treated with automated RBCX were compared to pooled and matched data from a database from another study in SCD; also an intrapatient comparison to growth rate before starting RBCX
Duration of study	Not reported. Study data ended in August 2011

	Age at start of treatment varied between 4.0-16.1 years and duration of RBCX from 1.2-13.2 years.
Patient population	Children with SCD receiving RBCX for >1year
Sample size	n=36
Inclusion criteria	Patients with HbSS or HbSβ
Exclusion criteria	Patients with HbSC
Intervention(s) (n =) and comparator(s) (n =)	For growth rate: • n=36 • n=1,868 children with SCD <20yrs age • n=64 children with SCD matched for age (±6 months), gender and growth at start of RBCX For peak height velocity: • n=24 children with SCD who began RBCX <14 yrs • n=43 children with SCD matched controls age 7-18 yrs
Baseline differences	A Wald test for linear mixed effects models was used to test for differences in the growth parameters between study subjects and matched controls. Comparator data was collected ~30 years prior to this study. There was a significant difference ($p<0.05$) in height and BMI between the study group and the pooled data, but not the matched group.
How were participants followed-up. Duration of follow-up, participants lost to follow-up	Chart data was collected at ≤6 month intervals from routine clinic attendance prior to RBCX and from RBCX visits post-treatment initiation; 66% of pre-RBCX observation were available. Duration of pre-RBCX data was ≤16.1 years Duration of RBCX treatment was ≤13.2 years Comparator anthropomorphic data was extracted from the Cooperative Study of Sickle Cell Disease (CSSCD) database (National Heart Lung Blood Institute)
Statistical tests	Wald test for linear mixed effects models
Primary outcomes	Z-score for growth rate, ago of peak height velocity

Study name	**q: Billard et al. 2013**
Objective	Evaluate the use of femoral catheters for automated RBCX in children
Location	France
Design	Unclear, but assume retrospective. Single arm observational study. Reported as a case series.
Duration of study	2004 to 2010
Patient population	Children with SCD and poor venous access, requiring RBCX

Sample size	n=18 patients, 443 procedures
Inclusion criteria	No additional criteria
Exclusion criteria	Not stated
Intervention(s) (n =) and comparator(s) (n =)	Femoral catheter and RBCX using Cobe Spectra system, n=18
Baseline differences	NA
How were participants followed-up. Duration of follow-up, participants lost to follow-up	Not stated. Retrospective evaluation of complications, SCD events and chelation therapy. Median 42 months (range 12-76 months) of treatment.
Statistical tests	Wilcoxon signed rank for pre-post treatment ferritin
Primary outcomes	Number of procedures, pre and post procedure HbS%, ferritin levels, RBC usage, complications

Study name	**r: Kalff et al. 2010**
Objective	Evaluate the effectiveness of the RBCX programme
Location	Australia
Design	Retrospective observational study. Reported as a case series.
Duration of study	10 years, Dec 1998 to Nov 2008
Patient population	Adults with SCD requiring regular RBCX
Sample size	N=13
Inclusion criteria	>18 years Complicated SCD despite maximal hydroxycarbamide, or therapy contraindicated or refused. Life threatening multi-organ failure crisis, or Acute chest syndrome, or ≥ 1 hospital admission/year for painful crises, or Pregnancy, or Silent cortical infarcts
Exclusion criteria	Not stated
Intervention(s) (n =) and comparator(s) (n =)	Cobe Spectra system RBCX n=13 NA
Baseline differences	NA
Follow up	Ongoing treatment programme
Statistical tests	Not reported
Primary outcomes	HbS acutely and prior to next exchange, procedure interval, acute events, related end-organ damage, complications, cost

Study name	**s: Ma et al, 2005**
Objective	Efficacy of IHD-RBCX compared to RBCX
Location	North Carolina, USA
Design	Not reported. For all procedures, the Gambro Spectra software was used to calculate volume of red cells needed and time required, whether or not IHD was used.
Duration of study	Not reported
Patient population	Teens and adults with SCD receiving chronic exchange for ≥12 months
Sample size	n = 7
Inclusion criteria	No additional criteria
Exclusion criteria	No additional criteria
Intervention(s) (n =)	68 procedures in 7 patients 58 procedures in 6 patients evaluated
Baseline differences	NA
How were participants followed-up. Duration of follow-up, participants lost to follow-up	Not reported
Statistical tests	The difference in RBC volume used was compared by logarithmic regression analysis to pre-procedure Hct, the difference in pre/post-RBCX Hct, and FCR.
Primary outcomes	Red blood cell volume savings as a function of haematocrit and FCR, calculated by the device.

Study name	**t: Masera et al. 2007**
Objective	Consider efficacy, safety and costs of an exchange transfusion program in high risk paediatric patients
Location	Italy
Design	Retrospective observational study. Some outcomes are reported as for a single arm study, other are compared to pre-RBCX values.
Duration of study	11 years, 1995 - 2006
Patient population	Children with SCD
Sample size	N=13 patients, 185 procedures
Inclusion criteria	High risk paediatric patients with SCD • RBCX every 3-6 months: children refused, or intolerant of, HU; previous stroke; high number of admissions despite simple transfusion; significant iron overload • RBCX+HU: symptomatic despite hydroxyurea; RBCX at <3 months intervals required for control
Exclusion criteria	Not stated

Intervention(s) (n =) and comparator(s) (n =)	Cobe Spectra system RBXC n=13 Some outcomes reported for larger cohort n=34 including n=13 with no regular treatment, n=5 receiving HU only or n=3 on simple transfusions.
Baseline differences	NA
Statistical tests	Not reported
Primary outcomes	RBCX procedures, hospital admissions, pain crises, complications, ferritin levels, RBC used, HbS%, Foetal Hb (HbF%)

Study name	**u: Sarode et al, 2011 / Myers et al, 2003**
Objective	Compare isovolemic haemodilution red blood cell exchange (IHD-RBCX) to conventional red blood cell exchange (C-RBCX)
Location	Texas, USA
Design	Retrospective observational before-and-after intrapatient comparative study using historical control (C-RBCX), plus theoretical contemporary comparison using device parameters
Duration of study	Sarode: All patients continuously enrolled between September 2001 to November 2008 Myers: Not reported, but assumed to cover the period from 2001 to ~2003.
Patient population	Adults with SCA, stable with history of thrombotic stroke
Sample size	Sarode: n = 23, 10 male, age 16-35 years at end of study; 3 of these excluded from analysis due to inadequate number of procedures performed Myers: n = 12, 6 male, age 8-29 years
Inclusion criteria	Sarode: History of stroke*, >1 C-RBCX procedure*, weight ≥25 kg, consent given, at least 1 year of follow-up (*reported in Myers).
Exclusion criteria	No additional criteria
Intervention(s) (n =) and comparator(s) (n =)	Sarode: n=20 IHD-RBCX, n=6 C-RBCX (historic control) Myers: n=12
Baseline differences	Sarode: Age at start of transfusion = 9.2 ± 6.3 years (median 6 years); patients in this group started to receive transfusion for secondary stroke prevention. Age at start of IHD-RBCX = 17.9 ± 6.3 years; patients in this group had received either simple transfusion or C-RBCX prior to this treatment. Myers: NA
How were participants followed-up. Duration of follow-up, participants	Sarode: Duration of IHD-RBCX treatment range 11 – 84 months (mean 54 ± 26.8 months, median 60.5 months)

lost to follow-up.	Myers: Not reported
Statistical tests	Sarode: 2-tailed student's t-test for paired samples. Myers: Not conducted
Primary outcomes	Sarode: Haematocrit*, HbS, procedure interval*, FCR, red blood cell volume*, procedure time*, ferritin levels*, chelation therapy*, adverse reactions*, costs (*reported in Myers).

Study name	**v: Shrestha, 2015**
Objective	To characterise the duration and complication rate of dual lumen Vortex ports in use for automated red cell exchange using Cobe Spectra system
Location	Wisconsin, USA
Design	Retrospective observational study
Duration of study	1 June 2008 – 1 July 2013
Patient population	Adult SCD patients undergoing scheduled automated RBCX
Sample size	318 procedures in 29 patients
Inclusion criteria	Indications for automated red cell exchange were secondary stroke prophylaxis and severe or frequent vaso-occlusive crises refractory to hydroxyurea.
Exclusion criteria	No additional criteria
Intervention(s) (n =)	318 procedures in 29 patients
Baseline differences	NA
How were participants followed-up. Duration of follow-up, participants lost to follow-up	Data collection procedures are not reported. Data collected for procedures between 1 June 2008 – 1 July 2013. Mean length of follow-up for a subgroup of patients (who had dual lumen ports placed, n=20) was 397 ± 263 days.
Statistical tests	Statistical tests were used to compare types of vascular access.
Primary outcomes (including scoring methods and timings of assessments)	Inlet speed, procedure duration, complication rates
Secondary outcomes (including scoring methods and timings of assessments)	Red blood cell use, rate of achieving target haematocrit, rate of achieving target HbS%

Study name	**w: Willis et al, 2011**

Objective	Report iron overload in patients on RBCX
Location	Boston, USA
Design	Retrospective case series
Duration of study	Not reported
Patient population	Young adults with SCD having monthly automated RBCX
Sample size	n = 5
Inclusion criteria	No additional criteria
Exclusion criteria	No additional criteria
Intervention(s) (n =)	5, number of procedures=63
Baseline differences	NA
How were participants followed-up. Duration of follow-up, participants lost to follow-up	Not reported. Duration of treatment = 6 – 22 months (reported erroneously as 'treatment interval')
Statistical tests	Not conducted
Primary outcomes	Ferritin, chelation therapy

Tables B6x-z Summary of methodology for observational studies: Spectra Optia system versus Cobe Spectra system comparison

Study name	**x: Perseghin et al (2013a) / Perseghin et al (2013b)***
Objective	Compare RBCX using Spectra Optia system with Cobe Spectra system
Location	Two centres, in Italy and Austria
Design	Observational analysis of data from consecutive patients.
Duration of study	Not clear. Data for Spectra Optia system were available from the two centres from March 2011 and May 2012; data for the comparator group were from "the months before" this.
Patient population	"High risk" sickle cell disease patients who underwent erythrocyte exchange procedures for either prophylactic or emergency treatment. Includes both adults and children.
Sample size	n=27, number of procedures=46 (2013a) n=19, number of procedures=33 (2013b)
Inclusion criteria	The group who underwent prophylactic treatment needed suitable peripheral venous access The group who underwent emergency treatment are described as patients not responding to hydration and/or analgesic therapy or presenting with acute chest syndrome or severe bone pain

Exclusion criteria	Not reported
Intervention(s) (n =) and comparator(s) (n =)	Intervention (Spectra Optia): n=15, number of procedures=25 Comparator (Cobe): n=12, number of procedures=21 *Perseghin 2013b*:* *Intervention (Spectra Optia): n=8, number of procedures=13* *Comparator (Cobe): n=11, number of procedures=20*
Baseline differences	Numbers of adults and children are not reported. There was no statistically significant difference in mean weight. However: in the Spectra Optia group, 4/15 (26%) of patients had a body weight less than 20kg. Median weight for these 4 patients was 18.5kg. Comparator (Cobe) group, 3/12 (25%) of patients had a body weight less than 30kg. Median weight for these 3 patients was 30kg. Proportion of procedures for prophylaxis (2012a) were not statistically different in either report.
How were participants followed-up. Duration of follow-up, participants lost to follow-up	Follow-up details are not reported. Observation appears to cover the pre- and post-procedural periods only.
Statistical tests	t-test or chi-square as applicable
Primary outcomes	Target achievement (Hct), pre- and post-procedure HbS, pre-procedure haematocrit*, red blood cell volume, procedure duration, ferritin, side effects

Study name	**y: Poullin et al, 2014**
Objective	To compare isovolemic haemodilution RBCX using the Spectra Optia system and Cobe Spectra system
Location	La Conception University Hospital, Marseille, France
Design	Retrospective observational, intrapatient comparison
Duration of study	Jan 2010 – Dec 2012
Patient population	Adults with SCD receiving chronic auto RBCX
Sample size	23 patients
Inclusion criteria	Not reported
Exclusion criteria	Not reported
Intervention(s) (n =) and comparator(s) (n =)	46 procedures with Spectra Optia system (2 per patient) 46 procedures with Cobe Spectra system (2 per patient)
Baseline differences	None

How were participants followed-up. Duration of follow-up, participants lost to follow-up	Data was obtained by database review.
Statistical tests	Repeated mixed model
Outcomes	Haematocrit, HbS pre and post procedure, blood volume processed, RBC exchange volume, RBC units, procedure duration, FCR

Study name	**z: Turhan et al, 2013**
Objective	Compare Spectra Optia system and Cobe Spectra system for red cell exchange procedures
Location	Turkey
Design	Not reported. Assume a retrospective observational audit of clinical data.
Duration of study	Not reported. Cobe Spectra system was used from 2008, Spectra Optia system was used in the majority of procedures from July 2010.
Patient population	SCD patients
Sample size	347 procedures, 232 patients
Inclusion criteria	Not reported
Exclusion criteria	Not reported
Intervention(s) (n =) and comparator(s) (n =)	Spectra Optia: 159 procedures, 105 patients Cobe: 188 procedures, 127 patients
Baseline differences	Cobe patients were slightly but significantly younger, 21.54 ± 11.24 years vs. 24.08 ± 12 years p=0.04.
How were participants followed-up. Duration of follow-up, participants lost to follow-up	Not reported
Statistical tests	Not reported
Primary outcomes	Success in achieving haematocrit levels; ability to reduce HbS concentration
Secondary outcomes	Procedure time, total blood volume processed, number of RBC units, platelet reduction rate, severe adverse events resulting in discontinuation of procedure

Tables B6aa-ad Summary of methodology for observational studies: automated RBCX versus top-up transfusion (TUT)

Study name	**aa: Adams et al. 1996**
Objective	Determine the advantages, complications, costs and efficacy of red blood cell exchange in young paediatric

	patients
Location	USA
Design	Retrospective before-and-after intrapatient comparison
Duration of study	Average of 16 months (range 6-20) RBCX
Patient population	Children requiring chronic RBCX
Sample size	N=10
Inclusion criteria	Children requiring chronic transfusions. n=9 SCD and previous stroke N=1 congenital dyserythopoietic anaemia
Exclusion criteria	Not stated.
Intervention(s) (n =) and comparator(s) (n =)	Cobe RBCX n=10 Simple transfusion n=10
Baseline differences	Patients placed in three groups: 1. n=3 patients on chelation 2. n=4 patients not on chelation due to allergy or noncompliance 3. n=3 patients began RBCX soon after CVA (0,0.5,0.9 years) with no iron overload
Follow up	Mean 16 months of RBCX (range 6-20), by chelation group 1. 20 months 2. 12-20 months 3. 6-9 months
Statistical tests	Not stated
Primary outcomes	Ferritin levels, exposure to donor blood, chelation therapy, alloimmunisation, costs

Study name	**ab: Fasano et al, 2015 / Kaushal et al, 2013 (see Table 6d above)**

Study name	**ac: Hilliard et al, 1998**
Objective	Compare erythrocytapheresis with simple transfusion
Location	Alabama, USA
Design	Prospective, non-randomised, before and after intrapatient comparison in patients transferred from simple transfusion to erythrocytapheresis with Cobe Spectra system. Only Cobe Spectra data is extracted and is treated as a single arm prospective study.
Duration of study	Study duration not reported. Observation period for simple transfusion was 1 year for 9/11 patients and was 1.2 (0.3 - 1.6) years for erythrocytapheresis.
Patient population	Teens and adults with SCA, a history of stroke and on

	chronic simple/partial transfusions. Age range 11-25 years.
Sample size	N= 11
Inclusion criteria	No additional criteria reported
Exclusion criteria	No additional criteria reported
Intervention(s) (n =	N = 11. Number of procedures not reported.
Baseline differences	None reported
How were participants followed-up. Duration of follow-up, participants lost to follow-up	Not reported. Observation period for simple transfusion was 1 year for 9/11 patients and was 1.2 (0.3 - 1.6) years for erythrocytapheresis. 1/11 had no data recorded for simple transfusion.
Statistical tests	Not conducted
Primary outcomes (including scoring methods and timings of assessments)	Blood utilisation, complications, efficacy, cost, iron load. Further details not reported.
Secondary outcomes (including scoring methods and timings of assessments)	Donor exposure. Further details not reported.

Study name	**ad: Singer et al. 1999**
Objective	Evaluate the use of red blood cell depletion/exchange compared with simple transfusion for children with sickle cell disease
Location	USA
Design	Unclear, assume retrospective observational before-and-after intrapatient comparative study
Duration of study	Average of 9 months (range 6-11), date not stated
Patient population	Children with SCD receiving RBCX for primary (n=4) or secondary (n=4) stroke prevention
Sample size	N=8
Inclusion criteria	Not stated
Exclusion criteria	Not stated
Intervention(s) (n =) and comparator(s) (n =)	Cobe RBXC n=8 , depletion-exchange protocol Simple transfusion n=8
Baseline differences	Age range 1-17 years Weight range 21-70 kg 4 had history of stroke, 4 patients at high risk of stroke based on Transcranial Doppler Ultrasound
Follow up	Patients monitored monthly

Statistical tests	Not reported
Primary outcomes	Units of blood transfused, exposure to donor blood, ferritin levels, chelation therapy, procedure duration

7.4.2 Provide details on data from any single study that have been drawn from more than one source (for example a poster and unpublished report) and/or when trials are linked this should be made clear (for example, an open-label extension to randomised controlled trial).

Kuo et al (2015) and Kuo et al (2012a) report the same study. Results are identical.

Fasano et al (2015) and Kaushal et al (2013) report the same study. Kaushal report data for 25 patients over an 18 month period and Fasano reports on 36 patients over a 44 month period.

Perseghin et al (2013a and 2013b) report the same study in a peer-reviewed journal article and what appears to be a brief journal report. The article reports data from 2 sites (Italy and Austria, n = 15) whereas we assume that the brief report relates only to data from a single site (Italy, n=11), but data in this report is minimal.

Quirolo et al (2015) and Quirolo et al (2014) report the same study. The 2014 conference abstract reports minimal numeric data but is identical to that in the 2015 paper.

Sarode et al (2011) and Myers et al (2003) appear to report patients taken from the same hospital population. Myers reports data for 12 patients over an unknown period. Sarode reports data for all patients from Sept 2001 with at least 1 year of follow-up data. There is substantial overlap in the methodology. We assume a significant amount of overlap in the patients included in these two reports.

Bavle et al (2012) and Bavle et al (2014) report data from the same study. In the conference abstract (2012) the authors report data from 38 patients, whereas in the journal article (2014) 2/38 patients are removed from the

analysis as they have the HbSC variant. There are also 2 fewer patients included in the peak height velocity comparison.

7.4.3 Highlight any differences between patient populations and methodology in all included studies.

The studies have been presented grouped according to whether (in the context of this scope) they are considered to be comparisons between automated and manual therapies, single arm Spectra Optia system or Cobe Spectra system studies (or a combination), or comparisons between automated and top-up transfusion. Three studies (Perseghin/Perseghin, Poullin, Turhan) compare Spectra Optia system versus Cobe Spectra system and are presented as support for the equivalence of the two devices for this intervention in this population.

All studies were observational. Only two studies were identified as prospective (Hilliard et al, 1998 and Quirolo et al 2015/2014), the others were all retrospective or were unclear. All appeared to use routinely collected clinical data. Ten studies were conducted in paediatric patients or teens (Adams, Baker, Bavle/Bavle, Billard, Dedeken, Duclos, Fasano/Kaushal, Masera, Singer, Woods), ten in adults (Kalff, Kuo/Kuo, Kuo 2012b, Poullin, Sarode/Myers, Shrestha, Sturgeon, Todd, Webb, Willis), seven in a mixed population (Cabibbo, Cararra, Hilliard, Ma, Perseghin/Perseghin, Quirolo/Quirolo, Trompeter), one in pregnant woman (Asma) and one was unclear (Turhan). Automated RBCX was delivered by either Cobe Spectra system or Spectra Optia system, using standard exchange or depletion/exchange protocols (as listed in Table B3).

Eight studies conducted intrapatient before-and-after comparisons, for example when patients were transitioned from manual or top-up transfusion to automated RBCX (Adams, Dedeken, Hilliard, Sarode/ Myers, Singer, Woods) or from exchange to depletion/exchange (Kuo 2012b). Sturgeon et al (2009) do not report what therapy patients received prior to automated RBCX. In these studies patients are inevitably older and likely to have progressed SCD in the intervention groups. In Cabibbo et al (2005) only patients with good

compliance and good venous access were able to receive automated RBCX instead of manual.

7.4.4 Provide details of any subgroup analyses that were undertaken in the studies included in section 7.4.1. Specify the rationale and state whether these analyses were pre-planned or post-hoc.

Duclos et al, 2013 performed a subgroup analysis on exchanges performed within 40 days of the previous treatment on the basis that 20 days is the usual interval required to keep HbS at about 30%. This appears to be a post hoc analysis.

Fasano et al (2015) reported a subgroup analysis of 23/26 patients who had ≥2 liver iron concentration measurements to determine iron overload.

Quirolo/Quirolo compared depletion/exchange with exchange and children with adults in their Spectra Optia study and included 12 patients in the safety analysis who had been treated during the lead-in phase from exchange to depletion/exchange.

Sturgeon et al (2009) compared patients with different frequencies of procedures: regular (at least every 8 weeks), regular with occasional breaks, 3 or fewer procedures per year and 4 or fewer procedures in total.

Todd et al (2015) reported a subgroup analysis for 19/50 patients who had serial liver MRIs to evaluate iron overload (liver iron concentration).

7.4.5 If applicable, provide details of the numbers of patients who were eligible to enter the study(s), randomised, and allocated to each treatment in an appropriate format.

NA - all comparative studies were retrospective observational studies.

7.4.6 If applicable provide details of and the rationale for, patients that were lost to follow-up or withdrew from the studies.

NA

7.5 Critical appraisal of relevant studies

Complete a separate quality assessment table for each study. A suggested format for the quality assessment results is shown in tables B7 and B8.

Table B7 Critical appraisal of randomised control trials - NA

Tables B8a-f Critical appraisal of observational studies: manual versus automated RBCX studies

Study name	**a: Cabibbo et al 2005**	
Study question	**Response yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Notes	Very few details of the study design are reported in this paper. Data collection methods are not described. We have assumed this is a retrospective review of routine clinical data. Patients underwent manual exchange because of poor compliance with the cell separator, or difficult venous access. There is a significant risk of selection bias but low risk of performance and assessment bias. The data is mostly presented as a case series and no statistical analysis is conducted. For summary data no indication of variance is provided. Patients receiving automated RBCX procedures were treated with 3 different apheresis devices, two of which are out of scope. However, procedure duration is reported separately for the Cobe Spectra system and this paper also provides evidence to support the difference in ferritin accumulation in automated procedures compared to manual.	

Study name	**b: Dedeken et al, 2014**	
Study question	**Response yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was the cohort recruited in an acceptable way?	Not clear	Patient selection is not reported. It is not reported whether all eligible patients were included. Significant risk of selection bias.
Was the exposure accurately measured to minimise bias?	Not clear	We assume that routine clinical data was used. Small risk of performance bias.
Was the outcome accurately	Not clear	We assume that routine clinical data was used. Small risk of assessment bias.

measured to minimise bias?		
Have the authors identified all important confounding factors?	Partially	Patient age and duration of therapy are reported.
Have the authors taken account of the confounding factors in the design and/or analysis?	Partially	Using intrapatient comparison balances some of the patient-specific confounders, however increasing age and size may have influenced results. This is not discussed by the authors.
Was the follow-up of patients complete?	Not clear	Not reported. Presumably follow-up continued to the end of the last reported procedure for each patient.
How precise are the results?		Confidence intervals are not reported.
Note	Device name is not reported but manufacturer and author have confirmed that Spectra Optia system was used.	

Study name	**c: Duclos et al 2013**	
Study question	**Response yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was the cohort recruited in an acceptable way?	Not clear	Criteria used to select the RBCX patients is not reported. The authors do not state that they were consecutive. Significant risk of selection bias.
Was the exposure accurately measured to minimise bias?	No	All of the intervention group were treated at one site, with the comparator group being treated at another site. This may have introduced bias. The authors acknowledge that there is a probable centre effect. They also note that practice varies markedly depending on the physician and the patient.
Was the outcome accurately measured to minimise bias?	Partially	Data is assumed to be routine clinical data. Small risk of assessment bias. Emphasis is given to the correlation between HbS levels and procedure interval, but this is not reported numerically, and is not statistically analysed.
Have the authors identified all important confounding factors?	Not clear	Patients were matched by age and weight. As noted above, other confounding factors may exist due to site differences.
Have the authors taken account of the confounding factors	Partially	Matching by age and weight should have addressed these potential confounders. No attempt was made to minimise potential site

in the design and/or analysis?		effects.
Was the follow-up of patients complete?	Not clear	It is not reported whether there were any missing data, other than post-procedure HbS, which was not included due to insufficient data.
How precise (for example, in terms of confidence interval and p values) are the results?		Confidence intervals are not provided.

Study name	**d: Fasano et al, 2015 / Kaushal et al, 2013**	
Study question	**Response yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was the cohort recruited in an acceptable way?	Not clear	It is not clear how patient records were selected, and whether or not they were consecutive. Significant risk of selection bias.
Was the exposure accurately measured to minimise bias?	Not clear	Retrospective review of medical records suggests small risk of performance bias. 'Partial ME' is not described
Was the outcome accurately measured to minimise bias?	Not clear	Retrospective review of medical records suggests small risk of assessment bias. Fasano 2015 reports 'averages'. It is unclear whether this is mean or median. Kaushal 2013 reports means for some of the outcomes.
Have the authors identified all important confounding factors?	No	No baseline data were provided. There is no explanation of criteria used to select the procedure type.
Have the authors taken account of the confounding factors in the design and/or analysis?	No	There is no indication that the authors took potential baseline differences into account, except that patients were matched for CEK antigen when comparing alloimmunisation rate.
Was the follow-up of patients complete?	Not clear	Length of follow-up was not reported.
How precise (for example, in terms of confidence interval and p values) are the results?		No confidence intervals or standard deviations are reported.
Note	Device is not named in the reports but the manufacturer has confirmed that the centre involved has a Spectra Optia. We have assumed that this was used in this study.	

Study name	e: Kuo et al, 2012 / Kuo et al, 2015	
Study question	**Response yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was the cohort recruited in an acceptable way?	Not clear	The study is described as a "retrospective observational cohort study" that was "conducted as part of a quality assurance audit". There is no indication that these records were consecutive or that all patients were included. There may therefore have been some selection bias.
Was the exposure accurately measured to minimise bias?	No	All of the intervention group were treated at one site, with the comparator group being treated at another site. This may have introduced performance bias. The authors assert that "both institutions adhere to the same clinical standards of comprehensive care, indications for chronic transfusion and [pre-procedure] HbS targets". They do however acknowledge "unknown systematic differences between the two cohorts" in the study limitations.
Was the outcome accurately measured to minimise bias?	Yes	Outcomes are based on objective laboratory tests. It is not clear whether tests were carried out at the same laboratory. Audit of routinely collected clinical data suggests small risk of assessment bias.
Have the authors identified all important confounding factors?	Not clear	Patients are separated into HbS targets of <30% and <50% depending on the indication for exchange therapy. Patient characteristics are reported.
Have the authors taken account of the confounding factors in the design and/or analysis?	Not clear	The authors adjusted for prescribed pre-treatment HbS target, and conducted multivariate logistic regression. It is not clear what potential confounders were included in this model.
Was the follow-up of patients complete?	No	4/21 patients in the comparator group were unable to receive the transfusion (in a total of 11/202 sessions), due to low steady-state haemoglobin. There were no patients in the intervention group to which this applied. The procedure was aborted in 3/199 of the intervention group procedures and 5/202 of the comparator group procedures, due to poor IV access or blocked line/port.
How precise (for example, in terms of confidence interval and p values) are		Some p values are highly significant. No confidence intervals are reported.

the results?		
Note	Device is not named in the reports but the manufacturer has confirmed that the centre involved has a Spectra Optia. We have assumed that this was used in this study. Patient numbers and study dates are equivalent for the 2015 paper and the 2012 conference abstract. There is a typographical error in the table in Kuo 2015 where the data for procedure interval has been reported incorrectly. Kuo 2012 provide some clarification for the results. The 2015 journal publication is a letter – it is not a structured report and not peer-reviewed.	

Study name	**f: Woods et al, 2014**	
Study question	**Response yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was the cohort recruited in an acceptable way?	Not clear	Patient selection is not reported but assume that all patients who met inclusion criteria were included. Small risk of selection bias.
Was the exposure accurately measured to minimise bias?	Not clear	Data collection is not reported. We assume that data is routine clinical data. Small risk of performance bias. Some patients received both erythrocytapheresis and manual exchange. It was therefore difficult to separate outcomes for the two procedures.
Was the outcome accurately measured to minimise bias?	Not clear	Data collection is not reported. We assume that data is routine clinical data. Small risk of assessment bias.
Have the authors identified all important confounding factors?	No	No baseline differences were reported.
Have the authors taken account of the confounding factors in the design and/or analysis?	No	The total sample group is separated and compared in multiple ways making interpretation difficult. Baseline characteristics do not appear to have been included in the analysis. The authors attribute an increase in complications for ECP to the use of a large bore double lumen port.
Was the follow-up of patients complete?	Not clear	It appears that procedural data were available for all included patients. Longer-term outcomes were not reported.
How precise are the results?		Median and inter-quartile ranges are reported.
Note	Device is not named in the report but the manufacturer has confirmed that the centre involved has a Spectra Optia. We	

	have assumed that this was used in this study.

Tables B8g-h Critical appraisal of observational studies: manual exchange single arm studies

Study name	**g: Carrara et al, 2010**	
Study question	**Response yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was the cohort recruited in an acceptable way?	Not clear	Patient selection is not described. Significant risk of selection bias.
Was the exposure accurately measured to minimise bias?	Not clear	The data is routinely collected clinical data. Minimal risk of performance bias.
Was the outcome accurately measured to minimise bias?	Not clear	The data is routinely collected clinical data. Quality checking of the records is described. Minimal risk of assessment bias.
Have the authors identified all important confounding factors?	Not clear	Patient characteristics are reported in supporting information. However, the timing of this data is not clear.
Have the authors taken account of the confounding factors in the design and/or analysis?	Not clear	Analysis is minimal and descriptive.
Was the follow-up of patients complete?	Not clear	Follow-up is described as ranging between 14 and 29 years. It is not clear how these data were obtained, and whether any may be missing.

Study name	**h: Webb et al. 2014**
Notes	Retrospective, single arm, cohort study over a 10 year period. Inclusion criteria stated. Outcomes reported are routine clinical measurements and are quantitative laboratory data with minimal risk of bias. Statistical methods reported. The procedure is not described in the abstract but the hospital website describes the manual RBCX procedure: http://jeffersonhospital.adam.com/content.aspx?productId=117&pid=1&gid=002923

Tables B8i-n Critical appraisal of observational studies: Spectra Optia system single arm studies

Study name	**i: Baker et al, 2013**	
Study question	**Response yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was the cohort recruited in an acceptable way?	Not clear	Patients selection is not described. Significant risk of selection bias.
Was the exposure accurately measured to minimise bias?	Not clear	Retrospective review of routinely collected clinical data. Small risk of performance bias.
Was the outcome accurately measured to minimise bias?	Not clear	Retrospective review of routinely collected clinical data. Small risk of assessment bias.
Have the authors identified all important confounding factors?		Use of spun HCT method for replacement fluid could contribute to not achieving target Hct.
Have the authors taken account of the confounding factors in the design and/or analysis?		No baseline data presented or described
Was the follow-up of patients complete?		Follow up to end of procedure only
How precise (for example, in terms of confidence interval and p values) are the results?		No CI or p values given.
Notes	There is little detail reported in this conference abstract. There is some confusion about the number of procedure/patients included in each result. 2/6 patients were excluded for crisis treatment and 5/52 procedures did not have post levels available.	

Study name	**j: Kuo et al, 2012b**	
Study question	**Response yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Notes	Little detail is reported in this conference abstract. Patient selection and data collection method is not reported. As the data is routinely collected clinical data and no subjective assessments were reported, a small risk of performance and assessment bias is assumed. Using an intrapatient comparison should have balanced some of the patient-specific confounders, however increasing age and potential changes in clinical practice over time may have influenced results. This is not discussed by the authors.	

Study name	k: Quirolo et al, 2015 / Quirolo et al, 2014	
Study question	**Response yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was the cohort recruited in an acceptable way?	Not clear	The type of treatment procedure (exchange or depletion/exchange) was decided by the investigator. Decision criteria are not reported, but it is noted that depl/RBC is only used in patients with a high Hct (so that the depletion cycle does not cause severe anaemia). It is not reported if all eligible patients were contacted for consent. Patients treated using depl/RBCX may have had a higher mean pre-procedure Hct than those who underwent RBCX. The pre-procedure Hct was not reported separately for these subgroups. Although inclusion criteria included acute treatments, all enrolled subjects were on a chronic exchange programme.
Was the *exposure* accurately measured to minimise bias?	Not clear	As noted above, selection bias may have affected which patients received each of the two procedure types. The authors do not report whether all of the five centres had access to both RBCX and depl/RBCX options. There may have been systematic differences between sites.
Was the *outcome* accurately measured to minimise bias?	Not clear	The majority of outcomes are based on objective laboratory tests. Tests were carried out at the same laboratory to maximise the consistency of the measurements. Investigator's subjective assessment of procedural success may be open to bias. It is not clear why summary peripheral blood counts before and after the procedure (Table 2) was reported for the enrolled population rather than the evaluable population. As statistical methods are not reported, it is not possible to establish whether these were appropriate.
Have the authors identified all important confounding factors?	No	Baseline differences are not reported, and may have influenced results.
Have the authors taken account of the confounding factors in the design and/or analysis?	Not clear	No reference is made to any adjustments for baseline differences.
Was the follow-up of	Yes	Efficacy analyses were carried out on data

patients complete?		from all evaluable subjects (n=60), suggesting that there were no failed procedures.
How precise (for example, in terms of confidence interval and p values) are the results?		Standard deviations suggest that some of the measures were quite variable, including replacement volumes of red blood cells, and proportion of HbS.

Study name	**l: Sturgeon et al, 2009**	
Study question	**Response yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was the cohort recruited in an acceptable way?	Not clear	Patient selection not reported. Not clear if all patients included. Significant risk of selection bias.
Was the exposure accurately measured to minimise bias?	Not clear	Analysis of routine clinical data suggests small risk of performance bias.
Was the outcome accurately measured to minimise bias?	Not clear	Analysis of routine clinical data suggests small risk of assessment bias.
Have the authors identified all important confounding factors?	Not clear	Little baseline data reported.
Have the authors taken account of the confounding factors in the design and/or analysis?	Not clear	Not stated
Was the follow-up of patients complete?	Not clear	Admission data for 67/74 patients
How precise are the results?	Partially	Range, SD and p value given for results
Note	Device is not named but the manufacturer has confirmed that the centre uses Spectra Optia system for RBCX procedures.	

Study name	**m: Todd et al, 2015**	
Study question	**Response yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Notes	Very little detail is reported in this conference abstract. Patient selection and data collection is not described.	

	Significant risk of selection bias. As routine clinical data is used the risk of performance and assessment bias is considered to be small. The device is not named, but Homerton Hospital uses a Spectra Optia system for automated red blood cell exchange procedures.

Study name	**n: Trompeter et al, 2015b**	
Study question	**Response yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Notes	Very little detail is reported in this narrative abstract. Numeric data is not reported. Device name is not reported but the manufacturer has confirmed that this centre own a Spectra Optia system, so we have assumed that this is used.	

Table B8o Critical appraisal of observational studies: Cobe Spectra system/Spectra Optia system combined single arm studies

Study name	**o: Asma et al 2015**	
Study question	**Response yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was the cohort recruited in an acceptable way?	Not clear	Patient selection is not described. Significant risk of selection bias.
Was the exposure accurately measured to minimise bias?	Not clear	The data is routinely collected clinical data. Minimal risk of performance bias.
Was the outcome accurately measured to minimise bias?	Not clear	The data is routinely collected clinical data. Quality checking of the records is described. Minimal risk of performance bias.
Have the authors identified all important confounding factors?	Not clear	Little baseline data for the groups is reported. No patient history reported.
Have the authors taken account of the confounding factors in the design and/or analysis?	Not clear	NA. Control group is out of scope.
Was the follow-up of patients complete?	Not clear	No reported loss of data in the RBCX group. Control group is out of scope.
Notes	The control group of patients not receiving any transfusion therapy is out of scope. This study is therefore considered as a single arm study for the Spectra Optia system /Cobe	

	Spectra system automated RBCX. Patients were treated using both devices and data is not reported separately. Four patients were treated with automated RBCX for vaso-occlusive crisis in the 1st trimester, whereas all procedures in the 2nd and 3rd trimester except one were conducted prophylactically. Data for crisis therapy is not reported separately. We have included this paper to address the subgroup of pregnant women as included in the NICE decision problem. The obstetric database mentioned did not start until 2004. It is unclear whether data prior to this is obtained, or whether the hospital data management system contained appropriate data.

Tables B8p-w Critical appraisal of observational studies: Cobe Spectra system single arm studies

Study name	**p: Bavle et al, 2014/ Bavle et al. 2012**
Notes	Z-scores are difficult to interpret for the reader but normalise the values to age-appropriate medians. The authors attempted to find 2 matched controls for each study subject but were only able to identify 1 for 8/36 patients for the growth rate comparison and 5/24 for the peak height velocity comparison. The intercept and slope of the z-scores are reported numerically, and the changes are also presented graphically and narratively. Inclusion and exclusion criteria are well-described reducing the risk of selection bias. The use of matched controls also reduces this risk. Data used is retrospective from routine clinic and treatment visits and is therefore at low risk of performance and assessment bias. The authors note the potential limitation of comparing with control data from 30 years previously. Pooled controls were taller and slimmer than the study group – this was corrected for by also using a matched control group. Bavle et al 2012 is a conference abstract that reports data from the same study but using slightly different patient and control numbers. Patients with HbSC do not appear to have been excluded and there are fewer study patients for the peak height velocity. The authors do not report the device name but the manufacturer has confirmed that this study used the Cobe Spectra system.

Study name	**q: Billard et al. 2013**
Notes	Retrospective, single arm, cohort study. Patients included consecutively. Outcomes reported are primarily routine clinical measurements and are quantitative laboratory data with minimal risk of performance and assessment bias. Method of data collation not reported.

Study name	**r: Kalff et al. 2010**
Brief quality	This is a retrospective study of 13 adult patients. Criteria for

appraisal	treatment with RBCX is given. It is assumed that all patients on the programme are included the in data, but not stated. Outcomes reported are presumed to be routine clinical measurements and are quantitative laboratory data with minimal risk of performance and assessment bias. Although the inclusion criteria suggest RBCX is used for crisis treatment, this is actually chronic treatment regimes for patients who suffer from frequent crises. Some outcomes are reported compared to pre-RBCX programme values for n=7 patients who did not receive transfusion therapy. The patient sample is separated into different subgroups according to the outcome reported..

Study name	**s: Ma et al, 2005**	
Study question	**Response yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Notes	Little detail is reported in this conference abstract. Patient selection and data collection is not reported. One patient was excluded from the analysis due to a post-haemodilution haematocrit of 32% (target <24%). As the saving in red blood cells is a calculated parameter this may be a prospective observational study. There is a significant risk of performance and assessment bias.	

Study name	**t: Masera et al. 2007**
Notes	This is a retrospective study of 34 patients, with most results being reported for 13 high risk patients. The recruitment methods are not stated and categorisation into treatment types may be subject to bias and alters during the study duration. It is unclear how all patients were treated. Outcomes are reported before and after a change in therapy, for each patient. Outcomes reported are presumed to be routine clinical measurements and are quantitative laboratory data with minimal risk of performance or assessment bias. During periods of RBCX 12/13 patients also received hydroxyurea, but the duration and timing of this is not reported. Reporting is poor and confusing. The sample is divided into subgroups for some analyses and numbers in each group are not always clear. Data presentation is often not clearly explained.

Study name:	**u: Sarode et al, 2011 / Myers et al, 2003**	
Study question	**Response yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was the cohort recruited in an acceptable way?	Yes	All patients continuously enrolled since Sept 2001 who have at least one complete year of follow up. Small risk of selection bias.

Was the exposure accurately measured to minimise bias?	Not clear	Retrospective comparison of routine patient data. Small risk of performance bias.
Was the outcome accurately measured to minimise bias?	Not clear	Retrospective comparison of routine patient data. Data collected prospectively for quality improvement/assurance purposes. Adverse events extracted from apheresis worksheets. Small risk of assessment bias.
Have the authors identified all important confounding factors?	Not clear	Patient baseline details reported in detail.
Have the authors taken account of the confounding factors in the design and/or analysis?	Not clear	Disproportionate number of adverse events ascribed to a small number of patients. No other subanalyses conducted.
Was the follow-up of patients complete?	Not clear	Median follow up was 60.5 months
How precise (for example, in terms of confidence interval and p values) are the results?	Yes	Results reported clearly and in detail. Individual patient data also reported for 20 IHD-RBCX patients.
Myers et al, 2003 - notes	Little detail is reported in this conference abstract. Patient selection and data collection are not reported. Comparison of IHD-RBCX is to historical and calculated values for RBCX, but it is unclear when these are used. Due to overlap in the authors and similarities in the data we conclude that there is substantial overlap between these reports. Most outcomes are similar, except the additional time for the IHD phase and the number of patients who have stopped chelation therapy.	

Study name	**v: Shrestha, 2015**	
Study question	**Response yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was the cohort recruited in an acceptable way?	Not clear	Patient selection is not reported. Significant risk of selection bias.
Was the exposure accurately measured to minimise bias?	Not clear	Data collection procedures are not reported.
Was the outcome accurately measured to	No clear	This is a retrospective comparison of routine patient data – no measurement bias assumed.

minimise bias?		
Have the authors identified all important confounding factors?	Not clear	Medications, type of venous access, and some patient demographics are reported.
Have the authors taken account of the confounding factors in the design and/or analysis?	Not clear	Confounding factors not included in analysis. The authors acknowledge the possibility that differences in vascular access used may have led to differences in results.
Was the follow-up of patients complete?	Yes	Immediate post-procedure outcomes only
Notes	Only data for the whole cohort relevant to this scope have been extracted.	

Study name	**w: Willis et al, 2011**	
Study question	**Response yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Notes	Little detail is reported in this conference abstract. Patient selection and data collection is not reported. There is significant risk of selection bias. As the data is assumed to be routinely collected clinical data a small risk of performance and assessment bas is assumed.	

Tables B8x-z Critical appraisal of observational studies: Spectra Optia system versus Cobe Spectra system comparisons

Study name	**x: Perseghin et al (2013a) / Perseghin et al (2013b)***	
Study question	**Response yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was the cohort recruited in an acceptable way?	Not clear	Consecutive patient records were included, reducing the potential for selection bias. However, criteria for determining whether the patient would be considered “high risk” are not specified.
Was the *exposure* accurately measured to minimise bias?	Not clear	The Cobe Spectra system is used as a historical control. It is not clear whether there might have been any other changes in clinical practices between the observational periods.
Was the *outcome* accurately measured to minimise bias?	Largely, yes	Most of the outcomes appear to be based on objective laboratory tests. It is not clear whether tests were carried out at the same laboratory. The term “Clinically relevant” side effects is not defined and may have been interpreted

		subjectively.
Have the authors identified all important confounding factors?	Not clear	Although not statistically significant, the imbalance in proportion of emergency patients in the two groups may have affected results.
Have the authors taken account of the confounding factors in the design and/or analysis?	Not clear	The results from patients treated as an emergency were not reported separately from the results of patients who underwent prophylactic treatment.
Was the follow-up of patients complete?	Yes	The authors report that all procedures were uneventful, suggesting that there were no incomplete procedures.
How precise (for example, in terms of confidence interval and p values) are the results?		Confidence intervals for HbS% would be relatively wide (based on the reported standard deviations). No sample size/power calculation is reported. With a total of 27 patients (15 in the Spectra Optia system group) the study may not have been sufficiently powered to detect clinically relevant differences between the two devices.

Study name	**y: Poullin 2014**	
Study question	**Response yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was the cohort recruited in an acceptable way?	Not clear	Patient selection not reported, significant risk of selection bias
Was the exposure accurately measured to minimise bias?	Not clear	Intrapatient comparison was used, however it is unknown how the exposure (procedure) was selected.
Was the outcome accurately measured to minimise bias?	Not clear	Retrospective comparison of routine patient data – no measurement bias assumed.
Have the authors identified all important confounding factors?	Not clear	Intrapatient comparison was used, but (e.g.) timing of different interventions is unreported
Have the authors taken account of the confounding factors in the design and/or analysis?	No	Details of analysis not reported
Was the follow-up of	Yes	Immediate post-procedure outcomes only

patients complete?		
Comments	Little detail is reported in this conference abstract.	

Study name	**z: Turhan et al, 2013**	
Study question	**Response yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Notes	Very little detail is provided in this conference abstract. Patient selection, data collection, analysis and even period of the study are not reported. It is unknown whether there was patient overlap between the two interventions. No patient information is provided other than age.	

Tables B8aa-ad Critical appraisal of observational studies: automated RBCX versus top-up transfusion (TUT) studies

Study name	**aa: Adams et al. 1996**
Notes	This is a retrospective study of 10 patients. The recruitment methods are not stated. There is significant risk of selection bias. Outcomes are reported before and after a change in therapy for each patient. Outcomes reported are presumed to be routine clinical measurements and are quantitative laboratory data with minimal risk of performance and assessment bias.

Study name	**ab: Fasano et al, 2015 / Kaushal et al, 2013 (see Table 8d above)**

Study name	**ac: Hilliard et al, 1998**	
Study question	**Response yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was the cohort recruited in an acceptable way?	Not clear	Patient selection is not reported.
Was the exposure accurately measured to minimise bias?	Not clear	Little information is provided about the planning of the procedures.
Was the outcome accurately measured to minimise bias?	Not clear	The test procedures and data collection are not described. The study is not blinded.
Have the authors identified all important confounding factors?	Not clear	The patient sample is small and mixed with regards to duration of transfusion and use of chelation therapy.

Have the authors taken account of the confounding factors in the design and/or analysis?	Not clear	No statistical analysis is conducted. Most data is presented graphically rather than numerically.
Was the follow-up of patients complete?	Not clear	The observation period following the change of therapy ranges from 0.3 – 1.6 years. Total duration of apheresis therapy 'to date' is also reported suggesting that this variation is due to different changeover dates rather than patients being lost to follow-up.
How precise (for example, in terms of confidence interval and p values) are the results?	Poor	Most data is presented graphically rather than numerically.
Notes	Most data is presented as per a case series, i.e. individual patient results. Much of the data is presented graphically and only a small amount of descriptive statistical analysis is conducted.	

Study name	**ad: Singer 1999**
Notes	This appears to be a retrospective study of 8 patients. The recruitment methods are not stated. There is a significant risk of selection bias. Outcomes are reported before and after a change in therapy for each patient. Outcomes reported are presumed to be routine clinical measurements and are quantitative laboratory data with minimal risk of performance and assessment bias. Reporting detail is low and no statistical testing is conducted.

7.6 Results of the relevant studies

7.6.1 Complete a results table for each study with all relevant outcome measures pertinent to the decision problem. A suggested format is given in table B9.

Table B9a-f Outcomes from published and unpublished studies: automated RBCX versus manual exchange

Study name		**a: Cabibbo et al, 2005**
Size of study groups	**Treatment (auto)**	206 procedures in 13 patients (Cobe Spectra system
	Control (manual)	188 procedures in 7 patients
Study	**Time unit**	Jan 1999 – Dec 2004

duration		
Type of analysis	**ITT/per protocol**	NA
Outcome	**Name**	**Red blood cell volume used**
Effect size	**Value (mean)**	6.1 units (auto, mixed devices) versus 1.8 units (manual)
Outcome	**Name**	**Procedure time**
Effect size	**Value**	70 mins (Cobe Spectra system) Manual not reported. No other details reported.
Outcome	**Name**	**Alloimmunisation and adverse events**
Effect size	**Value**	None of the patients developed complications related to the procedure or increased blood use. All patients showed clinical improvement. Adverse events were limited to symptoms of hypocalcaemia during automated RBCX. No patients developed clinically significant antibodies. One patient had a transfusion reaction of fever and haemolysis. 6/26 (23.1%) of their procedures had been carried out using the Cobe device. One patient died of acute chest syndrome. No patients developed new transfusion transmitted infection.
Outcome	**Name**	**Iron overload and iron chelation**
Effect size	**Value**	Manual: 7/7 had an increase in ferritin level, 4/7 of these patients were receiving iron chelation therapy. Auto (mixed devices): 7/13 patients had a reduction in ferritin, 5/13 had no change. None of these 12 patients were receiving iron chelation therapy. 1/13 patients had an increase in ferritin levels, and was receiving iron chelation therapy
Comments		HbS <30% was achieved after every procedure

Study name		**b: Dedeken et al, 2014**
Size of study groups	**Treatment**	n = 10 RBCX
	Control	n = 10 ME (historic control on same patients)
Study duration	**Time unit**	RBCX: Jan 2012 - June 2014 ME: 6 months prior to this period
Type of analysis	**ITT/per protocol**	Not reported.
Outcome	**Name**	**Target achievement HbS**
Effect size	**Value**	HbS remained in the target values for all patients (<30% in stroke risk, <50% for other indications).
Outcome	**Name**	**Level of abnormal haemoglobin (HbS%)**
Effect size	**Value (median, range)**	RBCX: 1st year 40% (28.5 – 42%) 2nd year 46% (31 – 48%) ME: 33.5% (25 - 42%)

Statistical test	**Type**	Friedman test or Dunn's Multiple Comparison Test
	p value	p=0.0002
Outcome	**Name**	**Duration of exchange procedure**
Effect size	**Value (median range)**	RBCX: 1st year 87.3 min (75.5 – 126min) 2nd year 91 min (64 – 154min) ME: 245 min (195 – 360min)
Statistical test	**Type**	Friedman test or Dunn's Multiple Comparison Test
	p value	P=0.0002
Outcome	**Name**	**Interval between procedures**
Effect size	**Value (median range)**	RBCX: 1st year 34 days (28 - 35.5) 2nd year 42 days (28 - 42) ME: 28 days (21 - 29)
Statistical test	**Type**	Friedman test or Dunn's Multiple Comparison Test
	p value	p<0.0001
Outcome	**Name**	**Red blood cells used**
Effect size	**Value (median range)**	RBCX: 1st year 32.2 ml/kg (27.4-36.1) 2nd year 30.0 ml/kg (26.8-36) ME: 18.3 ml/kg (15.1-20) RBCX: 1st year 67.0 units (49-120) 2nd year 65.5 units (38-137) ME: 39.5 units (15-79)
Statistical test	**Type**	Friedman test or Dunn's Multiple Comparison Test
	p value	p<0.0001 *(for both ml/kg and units)*
Outcome	**Name**	**Ferritin**
Effect size	**Value (median range)**	RBCX: 1st year 255 µg/l (52-811) 2nd year 148 µg/l (9-622) ME: 666 µg/l (182-1512)
Statistical test	**Type**	Friedman test or Dunn's Multiple Comparison Test
	p value	p<0.001
Outcome	**Name**	**Iron chelation**
Effect size	**Value**	2/10 patients on iron chelation, both stopped during RBCX treatment; 1 after 10 procedures, 1 after 1 procedure.
Outcome	**Name**	**Adverse events (procedure type not reported)**
	Value	9/181 (4.9%) procedures required medical intervention, of which 1 transient hypotension, 2 symptomatic hypocalcaemia, 2 transient headache, 2 fever, 1 nausea-vomiting (1), 2 abdominal pain.

Study name		**c: Duclos et al, 2013**
Size of study groups	**Treatment**	n=5, number of procedures=60
	Control	n=5, number of procedures=124

Study duration	**Time unit**	Not clear. Data collected between 2002 and 2008 for RBCX. Period was not defined for ME.
Type of analysis	**ITT/per protocol**	Not reported
Outcome	**Name**	**Pre-procedure HbS**
Effect size	**Value**	Not numerically reported. Pre-procedure HbS increases with time after exchange, but was much lower with RBCX than ME. Correlation between pre-procedure HbS and time after last exchange was better with RBCX.
Outcome	**Name**	**Pre-procedure haematocrit**
Effect size	**Value (median range)**	RBCX: 25.5% (19-31.6) ME: 27% (22-35)
Statistical test	**Type**	Student t-test or Mann Whitney *U* test
	p value	p<0.001
Other outcome	**Name**	**Pre-procedure HbS**
Effect size	**Value Median (range)**	RBCX: 47.5% (22-84) ME: 45.6% (20.6-81) *Subgroup of exchanges performed < 40 days after previous one:* RBCX: 32% (22-60) ME: 44.3% (20.6-63)
Statistical test	**Type**	Student t-test or Mann Whitney *U* test
	p value	Main comparison p=0.05 Subgroup comparison p<0.0001
Outcome	**Name**	**Procedure interval**
Effect size	**Value (median range)**	RBCX: 63 days (19-91) ME: 28 days (14-114)
Statistical test	**Type**	Student t-test or Mann Whitney *U* test
	p value	p<0.0001
Outcome	**Name**	**Blood volume transfused**
Effect size	**Value (median range)**	RBCX: 41 ml/kg (19.6-60) ME: 11.1 ml/kg (6.6-20) *Subgroup of exchanges performed less than 40 days after the previous exchange:* RBCX: 29 ml/kg (19.6-52) ME: 11 ml/kg (6.6-20)
Statistical test	**Type**	Student t-test or Mann Whitney *U* test
	p value	Main comparison p<0.0001 Subgroup comparison p<0.0001
Outcome	**Name**	**Adverse events**

Effect size	**Value**	RBCX: 3/60 (5%) procedures, of which 1 anxiety, 1 diffuse pain, 1 technical problem. None of the adverse events led to discontinuation of the procedure. Difficulties with venous access were recorded in 14/60 (23.3%) of RBCX procedures, but no central venous access was required. Adverse events in the ME group are not reported.
Outcome	**Name**	**Acute SCD complications**
Effect size	**Value**	RBCX 5 (0.045 per month), ~60 days since previous treatment ME: 4 (0.034 per month), ~25 days since previous treatment
Statistical test	**Type**	Student t-test or Mann Whitney *U* test
	p value	p=0.4
Comments		The authors report that "the evolution of iron overload, taking into account associated chelation, was variable but generally steady in all the procedures". "Cerebral injury" is also mentioned, but the interpretation of these outcomes is not clear.

Study name		**d: Fasano 2015 / Kaushal 2013** **(results for simple transfusion are not reported except where combined with ME)**
Size of study groups	**Treatment (RBCX, Spectra Optia)**	Fasano: n=10 Kaushal: n=5
	Control (partial ME)	Fasano: n=6 Kaushal: n=6
Study duration	**Time unit**	Fasano: 44 months Kaushal: 18 months
Type of analysis	**ITT/per protocol**	Not reported
Outcome	**Name**	**Average HbS**
Effect size	**Value (average)**	Fasano: RBCX: 34% Partial ME: 36% Kaushal: RBCX: 34% Partial ME: 38%
Statistical test	**Type**	Not reported
	p value	Not reported by Fasano 2015. Kaushal 2013: RBCX vs. partial ME/simple transfusion p=0.009
Outcome	**Name**	**Ferritin change** (ng/ml/month)
Effect size	**Value (mean range)**	Fasano: RBCX: -61 (-161 to +17) partial ME: +19 (-42 to +106) Kaushal: RBCX -142.3 (-590.1 to +136.8) Partial ME: +41.7 (-91.3 to +207.8)

Statistical test	**Type**	Fasano: Random effects model. Kaushal: Not reported.
	p value	Fasano: All procedures, p<0.0001 Kaushal: RBCX vs. partial ME/simple transfusion, p=0.02.
Outcome	**Name**	**Change in liver iron concentration** (mg/gm/year)
Effect size	**Value (mean range)**	Fasano: RBCX: -5.7 (-12.0 to +0.2) Partial ME: +1.6 (-9.2 to +10.9)
Statistical test	**Type**	Kruskal Wallis test
	p value	(All 3 procedures) p=0.0235
Other outcome	**Name**	**Alloimmunisation rates** (case/100 units)
Effect size	**Value**	Fasano: RBCX: 0.50 Partial ME/simple: 0.51 Kaushal: RBCX: 0.55 Partial ME: 1.1
Statistical test	**Type**	Not reported
	p value	Fasano: RBCX versus partial ME/simple transfusion, p=0.78 Kaushal: RBCX versus partial ME, p=0.57
Comments		

Study name		**e: Kuo et al, 2012a / Kuo et al, 2015**
Size of study groups	**Treatment**	n=30, number of procedures=199
	Control	n=21, number of procedures=202
Study duration	**Time unit**	May 2011- April 2012
Type of analysis	**ITT/per protocol**	Not reported. Procedures were either not attempted or abandoned in: • RBCX: 3/199 (1.5%) procedures • ME: 16/202 (7.9%) procedures It is not clear if procedures not attempted are included in the total number of procedures (199 and 202)
Outcome	**Name**	**Achievement of targets**
	Unit	Proportion of subjects achieving targets in more than 2/3 of their procedures.
Effect size	**Value**	A greater proportion of subjects having RBCX were able to consistently achieve targets compared to ME, although numbers were low in both groups: RBCX: 11/30 (36.7%) ME: 2/21 (9.5%) Kuo 2012: Unadjusted OR 5.5, 95% CI (1.07-28.22), p=0.048

		Kuo 2012/2015: Adjusted OR 4.72, 95% CI (0.89-25.20) Multivariate logistic regression: older age is associated with a higher likelihood of consistently achieving the target (OR 1.12, p=0.012).
Statistical test	**Type**	Chi-squared Adjusted odds ratio calculated using Mantel-Haenszel method Multivariate logistic regression to analyse covariates.
Outcome	**Name**	**Pre-procedure HbS** This outcome appears to be a median of the individual patient mean HbS% over a number of procedures, however this is not clearly stated.
Effect size	**Value (median range)**	RBCX: 50% (27-76) ME: 55% (16-72), p=0.162
	Variation	Distribution was reported as "highly variable both within and between subjects", but means were not found to be statistically different between the two groups (p=0.212).
Statistical test	**Type**	Chi-squared
Outcome	**Name**	**Post-treatment haematocrit**
Effect size	**Value (median range)**	RBCX: 0.31 (0.23-0.35) ME: 0.31 (0.25-0.38)
Statistical test	**Type**	Chi-squared
	p value	p=0.931
Outcome	**Name**	**Procedure duration**
Effect size	**Value**	RBCX: 115 mins ME: 257mins *Reported incorrectly in Table 1.*
Outcome	**Type**	Chi-squared
	p value	p<0.0001
Outcome	**Name**	**Prescribed treatment interval**
Effect size	**Value (median range)**	Kuo 2015: RBCX: 7.5 wks (4-8) ME: 4 wks (3-4) Kuo 2012: RBCX: 7.1 wks ME: 4.4 wks
Statistical test	**Type**	Mann-Whitney *U*
	p value	p<0.0001
Outcome	**Name**	**Procedure frequency**
Effect size	**Value (mean ± SD)**	RBCX: 6.66 ± 1.65 weeks ME: 4.86 ± 1.80 weeks
Statistical test	**Type**	Chi-squared
	p value	p=0.001
Outcome	**Name**	**Iron chelation**
Effect size	**Value**	RBCX: 7/30 (23.3%) patients ME: 6/21 (28.6%) patients

		Kuo 2012: RBCX was better than ME at maintaining a near zero iron balance due to considerable variability in the manual group (kurtosis statistic 13.221 ± 0.935 SE vs. 0.398 ± 1.121 SE)
Statistical test	**Type**	Chi-squared
	p value	p=0.673
Outcome	**Name**	**Red blood cells volume**
Effect size	**Value**	• RBCX: 241.1 ml/kg/year • ME: 127 ml/kg/year
Statistical test	**Type**	Chi-squared
	p value	p<0.001
Outcome	**Name**	**Red blood cells volume**
Effect size	**Value**	RBCX: 55 units per year ME: 32 units per year
Statistical test	**Type**	Chi-squared
	p value	p<0.0001
Outcome	**Name**	**Adverse events**
Effect size	**Value**	RBCX: 11 ME: 10 11/199 procedures in the RBCX group had to be converted to top-up transfusions due to low pre-procedure haematocrit versus none in the ME group. Kuo 2012: None of the patients in either group had new or progressive neurological events. Fever: RBCX 0/199; ME 2/202 Line sepsis: RBCX 0/199; ME 2/202 Dizziness: RBCX 5/199; ME 1/202 Citrate react.: RBCX 2/199; ME 0/202 Pruritis/hives: RBCX 1/199; ME 0/202 IV access: RBCX 3/199; ME 5/202
Statistical test	**Type**	Chi-squared
	p value	p=0.795
Comments		

Study name	**f: Woods et al, 2014**
Size of study groups	Overall (n = 38): • Received exclusively ECP, n=5 • Received exclusively ME, n=17 • Received both modalities, n=16 • Ever received ECP, n=21 • Never received ECP, n=17 Most recent 12-months for each participant: • 13 received ECP • 25 received ME

		• 5 patients switched from ECP to ME due to stenosis precluding double-lumen port replacement
Study duration	**Time unit**	Jan 2008 - Dec 2012
Type of analysis	**ITT/per protocol**	NA
Outcome	**Name**	**Achievement of HbS target**
Effect size	**Value (median IQR)**	ECP: 0.80 (0.40-1.0) ME: 0.50 (0.28-0.90)
	Note	Number of procedures for each arm is not reported Unclear if data for whole study period or most recent 12 months only
Statistical test	**Type**	Mann-Whitney *U*
	p value	p=0.27
Outcome	**Name**	**Ferritin concentrations**
Effect size	**Value (median IQR)**	ECP: 875 ng/ml (578-2659) ME: 1527 ng/ml (731-2568)
	Note	Number of procedures for each arm is not reported Unclear if data for whole study period or most recent 12 months only
Statistical test	**Type**	Mann-Whitney *U*
	p value	p=0.56
Outcome	**Name**	**Total duration of transfusion therapy**
Effect size	**Value (median IQR)**	Ever received ECP (n=21): 97 months (51.5-134) No ECP (n=17): 28 months (12.5-47)
Statistical test	**Type**	Mann-Whitney *U*
	p value	p<0.001
Outcome	**Name**	**Catheter complications**
Effect size	**Value**	ECP: 15/21 (71.4%) No ECP: 1/17 (5.8%) Odds ratio for patients who had ever received ECP: 40 (95%CI 4.29 - 372.4) p<0.001
Comments		Five subjects switched from erythrocytapheresis to manual exchange due to stenosis of the great vessels that precluded double-lumen port replacement.

Tables B9g-h Outcomes of observational studies: manual exchange single arm studies

Study name		**g:Carrara et al, 2010**
Size of study	**Treatment**	n = 7

groups		
Study duration	**Time unit**	Not clear. Data appear to be from the period between 1981 and 2010.
Type of analysis	**ITT/per protocol**	NA
Outcome	**Name**	**Interval between each procedure**
Effect size	**Value**	Range 45-90 days
Outcome	**Name**	**Ferritin and iron chelation**
Effect size	**Value**	6 patients had normal liver iron concentrations (mean 560, median 478, range 150 – 740). 1 patient started the program with iron overload (1353) and required iron chelation therapy. Units not reported, but assumed to be ng/ml.
Outcome	**Name**	**HbS change**
Effect size	**Value**	Pre-procedure: range 55-75% Post-procedure: range 35-50%
Outcome	**Name**	**Requirement for hospitalisation**
Effect size	**Value**	5 patients required hospitalisation during the study period, 4 with cholecystitis and 1 for vaso-occlusive crisis.
Comments		No patients experienced acute complications of SCD (such as acute chest syndrome). No patients experienced alloimmunisation.

Study name		**h: Webb et al. 2014**
Size of study groups	**Treatment**	Manual RBCX, n=15
Study duration	**Time unit**	10 years, January 2004 to December 2013
Pre-procedure Hct	**% (mean, range)**	25.1 (22.2 – 28.7)
Pre-procedure HbS	**% (mean, range)**	45.9 (26- 74.2)
Procedure interval	**weeks (mean, range)**	9.7 (4.0 – 22.1)
Procedure frequency	**per year (mean, range)**	7.1 (2.4 – 2.8)
Stroke	**events**	1 recurrent stroke
Stroke incidence	**per 100 patient years**	1.1
Hospital admissions	**per 100 patient years**	121
Notes	Hospital admissions were independent of HbS%, but correlated with weeks between procedures (Spearmans rho =0.61, p=0.0168) Hospital admissions correlated with weeks between procedures (Spearmans rho =0.7, p=0.0035), i.e. decreased adherence to	

	treatment schedule

Tables B9i-n Outcomes of observational studies: Spectra Optia system single arm studies

Study name		**i: Baker et al. 2013**
Size of study groups	**Treatment**	54 procedures in 6 patients total. 2 procedures in 2 patients for crisis therapy – excluded 52 procedures in 4 patients for regular RBCX every 4-5 weeks (5 procedures have no post-procedure values). 45 procedures in 4 patients evaluated
Study duration	**Time unit**	June 2010 to May 2012
Type of analysis	**ITT/per protocol**	NA
Outcome	**Name**	**Pre-procedure HbS**
Effect size	**Value (mean)**	40.37% (range 28.8 – 55.0)
Outcome	**Name**	**Post-procedure HbS**
Effect size	**Value (mean)**	10.9% (range 4 – 30)
Outcome	**Name**	**Pre procedure haematocrit**
Effect size	**Value (mean)**	0.269l/l (range 0.22 – 0.343)
Outcome	**Name**	**Post procedure haematocrit**
Effect size	**Value (mean)**	0.274l/l (range 0.23 – 0.34)
Outcome	**Name**	**Blood volume processed**
Effect size	**Value**	0.96 – 2.1l
	Adverse events	16 venous access pressure 4 vasovagal incidents 1 citrate reaction 1 extravasation
Comments		

Study name		**j: Kuo et al, 2012b**
Size of study groups	**Treatment**	7 patients, 74 depl/RBCX procedures
	Control	7 patients, 61 RBCX procedures
Study duration	**Time unit**	October 2009 – October 2011
Type of analysis	**ITT/per protocol**	Outcomes are compared on a intrapatient basis
Outcome	**Name**	**Pre-procedure HbS**
Effect size	**Value (mean)**	6/7: no significant difference (p=0.0589 to p=0.6870) 1/7: HbS higher with depl/RBCX, p=0.0071
Outcome	**Name**	**Post-procedure Hct**

Effect size	**Value (mean)**	5/7: no significant difference (p=0.1056 to p=0.8995) 2/7: Hct lower with depl/RBCX (p=0.0004 and 0.0148)
Outcome	**Name**	**Procedure interval**
Effect size	**Value (median)**	5 weeks (range 4-8 weeks)
Outcome	**Name**	**RBC volume reduction (by depl/RBCX)**
Effect size	**Value (mean)**	25 ml/kg/year
Outcome	**Name**	**Ferritin level, iron chelation**
Effect size	**Value**	Remained stable (p=0.2289). None of the patients were on iron chelation.
Outcome	**Name**	**Procedure duration**
Effect size	**Value (median)**	Depl/RBCX: 148 ± 51 mins RBCX: 147 ± 43 mins 7/7: no difference in median durations 6/7: no significant difference in mean duration 1/7: significant difference in mean duration (direction not reported)
Comments		11/135 procedures included an adverse event: 8/74 (10.8%) in depl/RBCX procedures 4/61 (6.6%) in RBCX procedures (p=0.3874) No significant difference in adverse event rate Citrate reaction (n=4) was commonest No incidence of treatment failure (SCD related complication) during study period.

Study name		**k: Quirolo et al, 2015 / Quirolo et al, 2014**
Size of study groups	**Evaluable population**	n=60
	RBCX	n=44
	Depl/RBCX	n=16
	Children	n=20
	Adults	n=40
	Safety	n=72
Study duration	**Time unit**	Not reported
Type of analysis	**ITT/per protocol**	Per-protocol (except safety analysis which was ITT)
Outcome	**Name**	**Target achievement: FCR**
Effect size	**Value (mean ± SD)**	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

Statistical test	**Type**	Not reported
	p value	No significant differences (p≥0.05)
Outcome	**Name**	**Target achievement: Hct (actual – target)**
Effect size	**Value**	mean ± SD - 1.03 ± 0.07 median (range) - 1.02 (0.9-1.3) Safety analysis (n=72) (mean ± SD): pre-procedure Hct 27.7% ± 4.39%, post-procedure Hct: 31.4% ± 2.61% (p<0.001).
Statistical test	**Type**	Not reported
	p value	Not reported except for safety analysis population, p<0.001.
Outcome	**Name**	**Post-procedure haematocrit**
Effect size	**Value (mean ± SD)**	• Evaluable population=31.4 ± 2.7% • RBCX sub-group=30.8 ± 2.6% • Depl/RBCX sub-group=32.9 ± 2.2% • Children sub-group=31.4 ± 3.0% • Adults sub-group=31.3 ± 2.5%
Statistical test	**Type**	Not reported
	p value	Significant difference between RBCX vs. depl/RBCX (p<0.05) No significant difference between children vs. adults (p≥0.05)
Outcome	**Name**	**HbS**
Effect size	**Pre-procedure value (mean ± SD)**	• Evaluable population=37.97 ± 12.81% • RBCX sub-group=37.00 ± 13.96% • Depl/RBCX sub-group=35.13 ± 8.68% • Children sub-group=39.83 ± 14.03% • Adults sub-group=34.24 ± 9.14%
	Post-procedure value (mean ± SD)	• Evaluable population=13.88 ± 6.03 • RBCX sub-group=14.11 ± 6.22 • Depl/RBCX sub-group=13.23 ± 5.64 • Children sub-group=14.7 ± 6.44 • Adults sub-group=12.24 ± 4.87
Statistical test	**Type**	Not reported
	p value	No significant differences (p≥0.05)
Outcome	**Name**	**Procedure duration**
Effect size	**Value (mean ± SD)**	• Evaluable population=90 ± 22 mins • RBCX sub-group=92 ± 24 mins • Depl/RBCX sub-group=86 ± 16 mins • Children sub-group=81 ± 16 mins • Adults sub-group=95 ± 24 mins

Statistical test	**Type**	Not reported
	p value	RBCX vs. depl/RBCX (p≥0.05) Children vs. adults (p<0.05)
Outcome	**Name**	**Total blood volumes processed**
Effect size	**Value (mean ± SD)**	Population not defined = 0.8 ± 0.2
Outcome	**Name**	**Red blood cell replacement volume**
Effect size	**Value - ml (mean ± SD)**	• Evaluable population=1895 ± 670 ml • RBCX sub-group=2016 ± 729 ml • Depl/RBCX sub-group=1562 ± 281 ml • Children sub-group=1449 ± 260 ml • Adults sub-group=2118 ± 702 ml
	Value - ml/kg (mean ± SD)	• Evaluable population=15.4 ± 5.1 ml/kg • RBCX sub-group=14.7 ± 5.0 ml/kg • Depl/RBCX sub-group=17.2 ± 4.9 ml/kg • Children sub-group=18.6 ± 3.5 ml/kg • Adults sub-group=13.8 ± 5.0 ml/kg
Statistical test	**Type**	Not reported
	p value	When comparing volume in ml there were significant differences (p<0.05) between: • RBCX vs. depl/RBCX • Children vs. adults. When adjusted for weight (ml/kg) the difference between RBCX and depl/RBCX was no longer significant (p≥0.05). The difference between children and adults was significant (p<0.05). Authors explain the difference as a disproportionate number of children in the depl/RBCX arm, who require smaller volumes. Therefore when adjusted for weight the difference is no longer apparent.
Outcome	**Name**	**Blood saved by depl/RBCX (calculated, intrapatient comparison)**
Effect size	**Value (median, range)**	n = 16: 134 ml (range 98-502) In 3/16 (18.8%) volume saved >250ml (full unit of blood)
Statistical test	**Type**	N/A
	p value	N/A
Outcome	**Name**	**Adverse events**

Effect size	**Value**	Serious adverse effects=0 Unexpected adverse device effect=0 Withdrawals from study due to adverse effects=0 Number of subjects reporting at least one adverse effect=13/72 (18.1%) Adverse effects reported at frequency of more than 5% were dizziness (n=6) and nausea (n=4), PLT count below $100x10^9$/L (n=4) All adverse events were mild to moderate in severity (grade 1, n=7; grade 2, n=6, grade 3&4, n=0) Subjects who reported adverse effects totalled 16.0% in the RBCX group, and 22.7% in the depl/RBCX group.
Comments		Quirolo 2014 abstract results were consistent with the 2015 paper.

Study name		**I: Sturgeon et al. 2009**
Size of study groups	**Treatment**	74 patients, 1578 procedures
	Control	n/a
Study duration	**Time unit**	September 1995 to January 2009
Type of analysis	**ITT/per protocol**	NA
Outcome	**Name**	**Volume of blood used**
Effect size	**Value (median)**	8 units (range 5-10.5)
Outcome	**Name**	**Hospital admission (**days per year)
Effect size	**Value (mean ± SD)**	Group A (n=25) pre: 34.8 ± 71.4 (range 0-365) post: 7.60 ± 9.87 (range 0-34) p<0.005 Group B (n=11) pre: 38.1 ± 40,98 (range 1-124) post: 34.1± 55.14 (range 0-163) p=0.53 Group C (n=5) pre: 45.3 ± 29.8 (range 0-75) post: 30.4 ± 24.48 (range 4-68) p=0.08 Group D (n=26) pre: 11.64 ± 15.33 (range 0-43) post: 42.26 ± 66.75 (range 3-190) p=0.161
Outcome	**Name**	**Mean serum ferritin levels**
Effect size	**Value (mean ± SD)**	Pre: 2523 ± 3198 µg/l (range 11-15990) Post: 2659 ± 3229 µg/l (range 21-14229)
Statistical test	**Type**	Not stated
	p value	P=0.10

Comments	Correlation between ferritin and patient's steady state Hb. Top-up of patients with low pre-exchange Hb increases patient's iron loading.

Study name		**m: Todd et al, 2015**
Size of study groups	**Treatment**	Automated RBCX
	Control	NA
Study duration	**Time unit**	Not reported, 36 months follow-up.
Type of analysis	**ITT/per protocol**	NA
Outcome	**Name**	**Liver iron at baseline / 12 / 18 / 24 / 36 mths (patients on chelation therapy)**
Effect size	**Value**	13.9 / 8.5 / 4.8 / 6.6 / 4.7 mg/m
Outcome	**Name**	**Liver iron at baseline / 12 / 18 / 24 / 36 mths (patients not on chelation therapy)**
Effect size	**Value**	1.8 / 1.4 / 1.4 / 2.2 / 1.5 mg/m
Outcome	**Name**	**Liver iron change (36 mths)**
Effect size	**Value**	-66%
Outcome	**Name**	**Average total RBC units used per transfusion**
Effect size	**Value**	10.5 units
Comments		

Study name		**n: Trompeter et al, 2015b**
Size of study groups	**Treatment**	70 patients
	Control	n/a
Study duration	**Time unit**	1 year pre and post intervention
Type of analysis	**ITT/per protocol**	n/a
Outcome	**Name**	Acceptability
	Value	Treatment was well tolerated, no increase in adverse events nor targets reached.
Outcome	**Name**	**Reduction in blood use**
	Value	Typically, for 70kg man: 2 units per procedure or 18 units per year for 6 weekly procedures Reduction in blood use most notable when increase in Hb not required.
Comments		2/70 patients had been sub-optimally exchanged using regular RBCX; depletion allowed all further exchanges to be performed on the scheduled days with sufficient units of blood to achieve desired targets.

Table B9o Outcomes of observational studies: Cobe Spectra system/ Spectra Optia system combined single arm studies

Study name		**Asma et al 2015**
Size of study groups	**Treatment**	43 procedures in 24 patients
	Control	13 patients
Study duration	**Time unit**	Jan 2000 – Mar 2013
Type of analysis	**ITT/per protocol**	Per-protocol
Outcome	**Name**	**Maternal complications**
Effect size	**Value**	3/24 (12.5%)
Outcome	**Name**	**Foetal complications**
Effect size	**Value**	1/24 (4.2%)
Outcome	**Name**	**Maternal death**
Effect size	**Value**	0/24 (0%)
Outcome	**Name**	**Blood volume processed**
Effect size	**Value (mean ± SD)**	5029.3 ± 543.8 ml (range 3693 – 6477)
Outcome	**Name**	**Pre-procedure haematocrit**
Effect size	**Value (mean ± SD)**	24.2 ± 3.5% (range 15.0 – 31.0)
Outcome	**Name**	**Post-procedure haematocrit**
Effect size	**Value (mean ± SD)**	27.5 ± 1.1% (range 26.0 – 31.0)
Outcome	**Name**	**Pre-procedure HbS**
Effect size	**Value (mean ± SD)**	74.5 ± 13.3% (range 40.8 – 99.0)
Outcome	**Name**	**Post-procedure HbS**
Effect size	**Value (mean ± SD)**	24.6 ± 10.1% (range 8.3 – 69.5)
Outcome	**Name (mean ± SD)**	**Red blood cells used**
Effect size	**Value (mean ± SD)**	6.2 ± 0.6 units (range 5.0 – 7.0)
Outcome	**Name**	**Replacement volume**
Effect size	**Value (mean ± SD)**	1893.9 ± 231.8 ml (range 1276 – 2482)
Outcome	**Name**	**Procedure time**
Effect size	**Value**	2-3 hrs
Outcome	**Name**	**Adverse events**
Effect size	**Value**	4/45 procedures included an adverse event: 1/4 anxiety, 1/4 allergic reaction, 2/4 paraesthesia (due to hypocalcaemia)

		Difficulties with venous access were recorded 8 times.
Outcome	**Name**	**Alloimmunisation and transfusion infection**
Effect size	**Value**	4/24 patients developed a positive IAT (indirect antiglobulin test) following the start of automated RBCX. (Data missing for 3/24 patients.) No transfusion-transmitted infections occurred.
Comments		

Tables B9p-w Outcomes of observational studies: Cobe Spectra system single arm studies

Study name		**p: Bavle et al, 2014/ Bavle et al. 2012**
Size of study groups	**Treatment**	Growth rate: n=36 Peak height velocity: n=24
	Control	Growth rate: n=1868 pooled, 63 matched Peak height velocity: n=43 matched
Study duration	**Time unit**	RBCX duration: 5.0±2.8 years (range 1.2-13.2) Age at RBCX: 9.6±4.6 years (range 4.0-16.1)
Type of analysis	**ITT/per protocol**	NA
Growth	**Intrapatient comparison**	Following the start of RBCX treatment, patients had a significant increase in the slope (change per month) of the z-score for weight, height and BMI (Wald test, p<0.05).
Growth	**Pooled & matched comparison**	Study subjects had a significant improvement in z-score slopes for height, weight and BMI compared to control groups. (Wald test, p<0.001)
Age at peak height velocity	**Matched comparison**	Females: study patients reached peak height velocity at a mean of 2 months earlier (n=16, p=0.94) Male: study patients reached peak height velocity at a mean of 11 months earlier (n=27, p=0.02)
Ferritin	**ng/ml (mean, range)**	33/36 no transfusion prior to RBCX (mean duration of RBCX was 63 months): RBCX: 681 (range 12-2359) 3/36 had transfusion prior to RBCX (mean duration of RBCX was 82 months): Transfusion: 2289 (672-3159) RBCX: 2216 (1207-3707)
Growth	**Comparison**	6/36 who received hydroxyurea for >2 years prior to RBCX had no significant improvement in height, weight or BMI during HU therapy (one-sample t-test)
Comments		The data here is taken from Bavle et al 2014.

Study name		**q: Billard et al. 2013**
Size of study	**Treatment**	n=18, 443 procedures

groups	**Control**	NA
Study duration	**Time unit**	6 years, median of 42 months (range 12-76 months)
Type of analysis		
Procedures	**Count**	median 23 procedures per patient
Procedure interval	**weeks**	8 weeks
Procedure duration		Catheter insertion + RBCX: <6 hours
Pre-procedure HbS	**%**	mean 39.3, median 38.2 (range 35-50)
Post-procedure HbS	**%**	mean 6.5, median 6.5 (range 3-12)
Ferritin	**ng/ml**	Start of treatment: mean 408, median 280 (range 22-1476) End of study: mean 429, median 294 (range12-2220)
	Statistical test	Wilcoxon signed rank, p=0.267
RBC use	**ml/kg**	mean 332 (range 280-370) per year mean 55 (range 47-62) per procedure
Complications/adverse events	2 children were agitated during catheter insertion and switched sedation method Difficult blood withdrawal precluded 1 procedure No infection or catheter-related bacteraemia No new organ damage or progression of existing organ damage 2/18 required hospital admission for minor painful crises (total=3) No alloantibodies developed	
Notes	3/18 ceased routine RBCX; 1 due to bone marrow transplant, 2 switched to hydroxyurea 17/18 without iron overload maintained stable ferritin without chelation	

Study name	**r: Kalff et al. 2010**		
Size of study groups	Cobe RBCX n=13 For before and after RBCX comparison: n=7 for pre-procedure HbS% n=6 for SCD events		
Study duration	10 years, Dec 1998 to Nov 2008		
Outcome	**Unit**	**Auto RBCX**	**Pre-programme**
RBC used	Units	5.7	NA
Procedure interval	Weeks (mean, range)	For n=12/13: 5.2 (4-6) For n=1/13 pregnancy: 3	NA

HbS post procedure	% mean (range)	n=13: 25.5 (18.5 – 32.6) n=7: 25.0 (18.5-32.6)	n=7: 76.9 (73.8 – 82.1)
HbS pre-procedure	% mean (range)	47.4 (40.7 – 59.3)	NA
Hospital admissions for SCD events (n=6, RBCX for painful crises)	Count	13 11/13 painful crises 2/13 ACS	60 57/60 painful crises 3/60 ACS
	Count/patient (median, range)	0.5 (0-6)	9 (2-16) (Incorrectly reported as 8)
	Events/year (mean, range)	1.9 (0.4 – 3.2) total 415 months follow-up (range 27-101 months)	0.2 (0 – 0.85) over 5 years
Hospital admissions for SCD events (during RBCX)	8/13 had no events following commencement of RBCX 5/13 patients had 16 events (total of 846 months follow up) 0/3 patients treated for ACS had a subsequent event 10/13 events during RBCX occurred in 2/6 patients		
Ferritin (µg/l) Reported according to pre-RBCX levels (µg/l) and treatments	Low, n=3	<600	<300
	Moderate, n=5	282 (69-361)	465 (311-582)
	High, n=3, previously treated with simple transfusion		
	n=2 (also treated with venesection and chelation)	900-7700	2700-10700
	n=1 (pregnancy)	Stable ~1900	Stable ~1900
Sickle cell disease-related end-organ damage	No stroke or multi-organ crises No evidence of new end-organ dysfunction or progression of previous end-organ dysfunction. Estimated glomerular filtration rate (eGFR) remained normal in 9 patients, 4 patients had subnormal eGFR prior to RBCX which remained stable or improved marginally.		
Complications	No echocardiographic evidence of cardiac dysfunction related to iron overload in any patient. All patients had normal baseline endocrine studies, no abnormalities developing during therapy. Clinically significant alloantibodies occurred in 3 patients No transfusion transmitted infections in any patients		
Venous access	Cubital fossa veins accessed for 10 patients Arterio-venous fistulae for 3 patients 2 line related infections requiring admissions		
Adverse events	Mild allergic reactions only No other adverse events		
Comments			

Study name		s: Ma et al, 2005
Size of study groups	**Treatment**	58 procedures in 6 patients
Study duration	**Time unit**	Not reported
Type of analysis	**ITT/per protocol**	NA
Outcome	**Name**	**Red blood cell volume saved by IHD**
Effect size	**Value (mean)**	2.9 ml/kg (median 2.0, range 0.9 - 9.0)
Outcome	**Name**	**Target HbS achieved**
Effect size	**Value**	Within 5% of target in 95% (55/58) procedures
Comments		Savings in RBC volume were related to pre-procedure Hct, but not FCR. A pre-procedure Hct of >32% was related to a saving of 1 unit pRBC (r^2=0.75).

Study name		t: Masera et al. 2007		
Size of study groups	**Treatment**	Cobe RBXC n=13 Some outcomes reported for larger cohort n=34 with no regular treatment, receiving HU or simple transfusions		
Study duration	**months**	Average 9 months (range 6-11) (Not stated if mean or median		
RBCX procedures per year	Count (mean, range)	2.6 (1.1 – 4)		
RBC use	var	<10 units or ~30ml/kg per procedure		
SCD events		**During RBCX + HU (n=12)**	**During RBCX only (n=13)**	**Pre RBCX (n=13)**
Hospital admissions	Count /year (mean, range)	0.24 (0-1) 8/12 patients had no admissions	0.69 (0-1.8) 2/13 patients had no admissions	1.7 (0.2-4)
Pain Crises	Count/year (mean, range)	1.79 (0-5.5)	Not reported	4.8 (0.2-12)
Ferritin (n unknown)	ng/ml	915 (270-1866)		1175 (45-2648)
Chelation	Count	1 patient discontinued chelation following 5 years of RBCX 3 patients started chelation following 4, 6 and 10 years of RBCX 4 remained on chelation at the end of the study period		
Pre-procedure	**% (mean, range)**	63 (49-83) – last procedure		

HbS		
Post-procedure HbS	**% (mean, range)**	20 (7-34) – last procedure
Comments	No patients developed alloantibodies as a consequence of the prophylactic RBCX treatment; 3 had developed alloantibodies during pre-RBCX treatment. No clinically significant side effects observed during the procedures.	

Study name		**u: Sarode et al, 2011 / Myers et al, 2003** (Data is from Sarode et al, 2011 unless otherwise stated)
Size of study groups	**Treatment**	Sarode: 20 patients analysed (3 excluded from original 23) Myers: 12 patients
	Control	Sarode: 6 patients (historical control), 20 patients (calculated data) Myers: 12 patients (assumed, unclear in abstract)
Study duration	**Time unit**	Sarode: Sept 2001 to Nov 2008 Myers: Not reported
Type of analysis	**ITT/per protocol**	Sarode: Per protocol, retrospective review of clinical practice
Outcome	**Name**	**Target achieved**
Effect size	**Value**	Sarode: Pre-procedure target of Hct >23% met in 92% of planned procedures (582/631) Myers: Post-IHD Hct variation from target was 3.2 ± 6.2%. Post-procedure Hct variation from target Hct was 7.2 ± 5.2%. Sarode: 582/631 planned procedures were completed Myers: 93/104 planned procedures were completed
	Comment	All unsuccessful procedures were due to problems with peripheral venous access.
Outcome	**Name**	**Pre-procedure haematocrit (n = 617)**
Effect size	**Value (mean ± SD)**	27.8 ± 2.4% (median 28.0, 23.0-33.2)
Outcome	**Name**	**Post-procedure haematocrit (n = 581, n=93*)**
Effect size	**Value (mean ± SD)**	Sarode: 32.8 ± 1.6% (median 32.9, range 30.4 – 36.6) Myers: 7.2 ± 5.2 % difference from target Hct
Outcome	**Name**	**Pre-procedure HbS (n = 574)**
Effect size	**Value (mean ± SD)**	41.8 ± 6.1% (median 43.0, range 30.6 – 52.4)
Outcome	**Name**	**Post procedure HbS (n = 569)**
Effect size	**Value (mean ± SD)**	9.8 ± 2.4% (median 9.9, range 6.7 – 16.4)
Outcome	**Name**	**Number of procedures per patient**

Effect size	**Value (mean ± SD)**	Procedures: 29.3 ± 14.5 (median 34.5, range 8-55) Successful procedures: 28.9 ± 14.2 (median 34, range 7-49). All non-successful procedures due to venous access problems.
Outcome	**Name**	**Interval between procedures**
Effect size	**Value (mean ± SD)**	Sarode: IHD-RBCX: 52.9 ± 6.5 days (median 52.7, range 44.6-74.5) For 6 patients with before and after data: C-RBCX 37 ± 7.0 days versus IHD-RBCX 52.9 ± 6.5 days (p<0.01) Myers: RBCX 40 days versus IHD-RBCX 49 days (median)
Outcome	**Name**	**Number of procedures per patients per year**
Effect size	**Value (mean)**	IHD-RBCX: 7.0 C-RBCX: 9.3
Outcome	**Name**	**Fraction of cells remaining (FCR, target 30%, n = 564, n=93*)**
Effect size	**Value**	Sarode: 23.8 ± 5.2%, median 23.9%, 15.2 – 38.6) Myers: 21%
Outcome	**Name**	**Red blood cell volume**
Effect size	**Value (mean ± SD)**	Sarode: IHD-RBCX: 35.5 ± 4.1 ml/kg (median = 36.0) Sarode: C-RBCX: 39.5 ± 4.6 ml/kg (median = 40.4, calculated) Myers: IHD-RBCX: 37 ml/kg Myers: RBCX: 41 ml/kg
	95% CI	-4.436 – 3.514, p<0.0001
Outcome	**Name**	**Red blood cell volume**
Effect size	**Value (mean)**	IHD-RBCX: 8.4 units
Outcome	**Name**	**Red blood cell volume saved by using IHD-RBCX**
Effect size	**Value (mean)**	Sarode: 1.0 unit/procedure (median 1.0, range 0.5–1.7) 10/20 patients saved >1.0 unit per procedure 30.5 units per patient per year Myers: Median 255 ml (range 111-459)
Outcome	**Name**	**Procedure run time calculated**
Effect size	**Value**	IHD-RBCX: 103.9±12.4 min C-RBCX: 107.3±6.7 min
	Comment	Sarode: Addition procedure activities added 3-4 min to IHD-RBCX, so roughly equivalent. Myers: IHD added median 24 mins to procedure time.
Outcome	**Name**	**Ferritin (IHD-RBCX)**
Effect size	**Value (mean)**	Start: 2977 (median 1933) End: 2885 (median 1922)

	Sarode note	9/20 patients showed an increase in ferritin 8/20 patients showed a decrease in ferritin
	Myers note	“a significant decrease in iron burden”
Outcome	**Name**	**Iron chelation therapy**
Effect size **(n = 20)**	**Value**	3 patients never required iron chelation (discontinued during C-RBCX) 2 patients discontinued iron chelation (1 of which had little change in ferritin level at ~580 ng/ml) The other 15 patients showed “marginal or no improvement” in ferritin level and are all on oral chelation
	Myers note	5/12 patients have stopped chelation therapy and 3/12 have reduced treatment days
Other outcome	**Name**	**Adverse events** IHD-RBCX: n=594 procedures, C-RBCX: n=112 (historical, or where IHD-RBCX not performed due to Hct <23%)
Effect size	**Value**	Overall: IHD-RBCX: 18.5% (109/594), C-RBCX: 13.5% (15/112) Allergic reactions: IHD-RBCX: 26% (28/109), C-RBCX: 60% (9/15) Citrate reactions (mild): IHD-RBCX: 34% (38/109), C-RBCX: 27% (4/15) Citrate reactions (moderate): IHD-RBCX: 6% (7/109), C-RBCX: 0% (0/15) Vasovagal reactions (mild): IHD-RBCX: 23% (25/109), C-RBCX: 7% (1/15) Vasovagal reactions (moderate): IHD-RBCX: 5% (5/109), C-RBCX: 0% (0/15) Other: IHD-RBCX: 5.5% (6/109), C-RBCX: 7% (1/15)
	Sarode notes	2 patients account for 28/45 (57%) of citrate reactions 2 patients account for 20/30 (67%) of vasovagal reactions
	Myers notes	No difference in incidence of adverse events
Other outcome	**Name**	**Development of new alloantibodies**
Effect size	**Value**	8/20 alloimmunised prior to program 2 of these developed new alloantibodies None of remaining 12 developed alloantibodies
Other outcome	**Name**	**Recurrence of clinical stroke**
Effect size	**Value**	No recurrence in median follow up of 60.5 months
Comments		

Study name		v: Shrestha 2015
Size of study groups	**Treatment**	318 procedures in 29 patients
Study duration	**Time unit**	1 June 2008 – 1 July 2013
Type of analysis	**ITT/per protocol**	Per protocol
Outcome	**Name**	**Procedure duration**
Effect size	**Value (mean ± SD)**	2.0 ± 0.7 hours
Outcome	**Name**	**Red blood cells used**
Effect size	**Value**	6.3 ± 1.7 units
Outcome	**Name**	**Target achievement of Hct, success rate**
Effect size	**Value**	87%
Outcome	**Name**	**Target achievement of HbS%, success rate**
Effect size	**Value**	95%
Outcome	**Name**	**Procedural complication rate**
	Description	The authors report that “about 50% of dual lumen port procedures [n=20] resulted in at least 1 access alarm that required nursing intervention, whereas only 15% of peripheral procedures [n=7] and no temporary catheter procedures [n=12] resulted in similar issues”.
Outcome	**Name**	**Adverse outcomes**
	Description	Seven vortex ports were removed, 6 due to infection, 1 due to malfunction. Mean time to removal was 171 days. No adverse outcomes in temporary central venous catheters (n=12) or peripheral vein catheters (n=7).
Comments		

Study name		w: Willis et al, 2011
Size of study groups	**Treatment**	n = 5
	Control	NA
Study duration	**Time unit**	Duration of therapy is 6 – 22 months
Type of analysis	**ITT/per protocol**	NA
Outcome	**Name**	**Ferritin**
Effect size	**Value (mean ± SD)**	Start: 2223 ± 1729 (median 1297, range 1035 – 5085) End: 1494 ± 1580 (median 722, range 12 – 3808) Reduction: 730 ± 421 (median 575, range 209 – 1277)
Outcome	**Name**	**Chelation therapy**

Effect size	**Value**	4/5 patients
Comments		All patients were non-compliant or intolerant of chelation therapy or had reached a plateau in decreasing iron stores.

Tables B9x-z Outcomes of observational studies: Spectra Optia system versus Cobe Spectra system comparisons

Study name		**x: Perseghin et al (2013a) / *Perseghin et al (2013b)***
Size of study groups	**Treatment (Spectra Optia)**	n=15, number of procedures=25
	Control (Cobe)	n=12, number of procedures=21
Study duration	**Time unit**	Not reported
Type of analysis	**ITT/per protocol**	Not reported. Results were available for all patients.
Outcome	**Name**	**Target achievement: Hct**
Effect size	**Value (mean ± SD)**	Approximate values from graph indicate: Spectra Optia: 101% ± 4%, Cobe: 100% ± 8%
Statistical test	**Type**	Chi-squared
	p value	p=0.606
Outcome	**Name**	**Pre- /post-procedure HbS**
Effect size	**Value (mean ± SD)**	Approximate values form graph indicate: Pre-procedure: Spectra Optia: 60% ± 16%, Cobe: 63% ± 12% Post-procedure: Spectra Optia: 23% ± 7%, Cobe: 20% ± 5%
Statistical test	**Type**	Chi-squared
	p value	Difference between Spectra Optia and Cobe: *Pre-procedure* p=0.518, *Post-procedure* p=0.344
Outcome	***Name***	***Pre-procedure haematocrit****
Effect size	***Value (mean ± SD)***	*Spectra Optia, 29.9 ± 5.3, Cobe, 28.0 ± 5.8*
Statistical test	***Type***	*Not reported*
	p value	*p=0.35*
Outcome	**Name**	**Number of red blood cell units used**
Effect size	**Value (mean ± SD)**	Spectra Optia: 6.2 ± 2.4 units, Cobe: 6.6 ± 1.5 units
Statistical	**Type**	Chi-squared

test	**p value**	p=0.55
Outcome	***Name***	***Volume of red blood cells used****
Effect size	***Value (mean ± SD)***	*Spectra Optia: 29.4* ± 6.8 ml/kg, *Cobe: 29.7* ± 7.7 ml/kg
Statistical test	***Type***	*Not reported*
	p value	*p=0.91*
Outcome	**Name**	**Procedure length**
Effect size	**Value (mean ± SD)**	Spectra Optia: 101 ± 28, Cobe: 99 ± 24
Statistical test	**Type**	Chi-squared
	p value	p=0.79
Outcome	**Name**	**Ferritin levels**
Effect size	**Value**	Spectra Optia: 935 ± 717% , Cobe: 1257 ± 1399%
Statistical test	**Type**	Chi-squared
	p value	p=0.97
Outcome	**Name**	**Side effects**
Effect size	**Value**	The authors report that no clinically relevant, treatment-related side effects were observed in the two groups. Two patients in the comparator (Cobe) group had transient paraesthesia.
Comments		**Outcomes that were only reported in Perseghin 2013b.*

Study name		**y: Poullin 2014**
Size of study groups	**Treatment (Spectra Optia)**	46 procedures, 23 patients (2 procedures per patient)
	Control (Cobe)	46 procedures, 23 patients (2 procedures per patient)
Study duration	**Time unit**	Jan 2010 – Dec 2011
Type of analysis	**ITT/per protocol**	Per protocol
Outcome	**Name**	**Procedure duration**
Effect size	**Value**	Spectra Optia = 94.3 ± 17 mins; Cobe = 100.2 ± 22 mins
Outcome	**Name**	**Abnormal Hb pre-procedure**
Effect size	**Value**	Spectra Optia = 51.2 ± 11%; Cobe = 51.1 ± 10%
Outcome	**Name**	**Abnormal Hb post-procedure**
Effect size	**Value**	Spectra Optia = 19 ± 5%; Cobe = 18.8 ± 5%
Outcome	**Name**	**Fraction of cells remaining (FCR)**
Effect size	**Value**	Spectra Optia = 38.3 ± 7%; Cobe = 37.9 ± 7%
Outcome	**Name**	**Haematocrit**

Effect size	**Value**	Spectra Optia = 29.9 ± 4%; Cobe = 28.8 ± 3%
Outcome	**Name**	**Red blood cells used**
Effect size	**Value**	Spectra Optia = 1817 ± 270 ml; Cobe = 1746.6 ± 271 ml ‡
Outcome	**Name**	**Red blood cells used**
Effect size	**Value**	Spectra Optia = 6.1 ± 1 units; Cobe = 6.1 ± 1 units
Outcome	**Name**	**Blood volume processed**
Effect size	**Value**	Spectra Optia = 4126 ± 795 ml; Cobe = 4298 ± 787 ml
Comments		P values not reported, but all results not significantly different except ‡ 'A few mild transfusion-related shiver-hyperthermia' events were noted.

Study name		**z: Turhan et al, 2013**
Size of study groups	**Treatment (Spectra Optia)**	159 procedures, 105 patients
	Control (Cobe)	188 procedures, 127 patients
Study duration	**Time unit**	Not reported
Type of analysis	**ITT/per protocol**	Per protocol
Outcome	**Name**	**Post-procedure Hct compared to target haematocrit**
Effect size	**Value** Target / actual	Spectra Optia: 27.34 ± 2.33% / 28.11 ± 4.21% Cobe: 26.9 ± 1.99% / 27.53 ± 3.2%
Outcome	**Name**	**HbS change**
Effect size	**Value**	Spectra Optia: -68.65 ± 17.23%; Cobe: -73.96 ± 22.43%
Outcome	**Name**	**Pre-procedure HbS**
Effect size	**Value**	Spectra Optia: 73.44 ± 20.05%; Cobe: 73.96 ± 19.98%
Outcome	**Name**	**Post-procedure HbS**
Effect size	**Value**	Spectra Optia: 23.6 ± 14.10%; Cobe: 22.43 ± 13.48%
Outcome	**Name**	**Pre-procedure Hct**
Effect size	**Value**	Spectra Optia: 24.54 ± 8.89%; Cobe: 24.18 ± 4.17%
Outcome	**Name**	**Procedure duration**
Effect size	**Value**	Spectra Optia: 99 ± 26.32 mins; Cobe: 114 ± 31.48 mins
Outcome	**Name**	**Fraction of cells remaining (FCR)**
Effect size	**Value**	Spectra Optia: 28.86 ± 6.09%; Cobe: 25.74 ± 7.63%
Outcome	**Name**	**Platelet reduction**

Effect size	**Value**	Spectra Optia: 53.52 ± 13.80%; Cobe: 51.83 ± 20.44%
Outcome	**Name**	**Red blood cells used**
Effect size	**Value**	Spectra Optia: 6.67 ± 2.25 units; Cobe: 6.72 ± 2.55 units
Outcome	**Name**	**Blood volume processed‡**
Effect size	**Value**	Spectra Optia: 4440 ± 1639 ml; Cobe: 4836 ± 1999 ml, ‡p<0.05
Outcome	**Name**	**Red blood cell volumes exchanged**
Effect size	**Value**	Spectra Optia: 1.31 ± 0.38; Cobe: 1.51 ± 0.44
Outcome	**Name**	**Number of severe adverse events (Grade 3)**
Effect size	**Value**	Spectra Optia: 3/159; Cobe: 0/188
Comments		Statistical test not reported. P values not reported for non significant results. All result not significantly different except ‡

Tables B9aa-ad Outcomes of observational studies: Automated RBCX versus top-up transfusion (TUT)

Study name		**aa: Adams et al. 1999**			
Size of study groups	**Treatment**	Cobe RBCX n=8			
	Control	Simple transfusion n=8			
	Analysis	Before and after intrapatient study. Analysis not reported.			
Study duration	**months**	Average of 16 months (range 6-20) RBCX			
Outcome	**Unit**	**Group**	**Auto RBCX**	**Simple**	
RBC used	units / year (mean)	Group1	61	34	
		Group2	54	28	
		Group3	43	n/a	
Ferritin	ng/ml	Group1	567- 2857	2247- 7373	3/3 decrease 1/3 stops chelation
		Group2	1870- 7623	1465- 7640	2/3 stable 1/3 sig. decrease
		Group3	416- 931	446- 906	3/3 stable
Comments		No increase in alloimmunisation seen.			

Study name		**ab: Fasano 2015 / Kaushal 2013** **(results for ME are not reported except where combined with TUT)**
Size of study groups	**Treatment (RBCX, Spectra Optia)**	Fasano: n=10 Kaushal: n=5
	Control (TUT)	Fasano: n=20

		Kaushal: n=14
Study duration	**Time unit**	Fasano: 44 months Kaushal: 18 months
Type of analysis	**ITT/per protocol**	Not reported
Outcome	**Name**	**Average HbS**
Effect size	**Value (average)**	Fasano: RBCX: 34% TUT: 33% Kaushal: RBCX: 34% TUT: 34%
Statistical test	**Type**	Not reported
	p value	Not reported
Outcome	**Name**	**Ferritin change** (ng/ml/month)
Effect size	**Value (mean range)**	Fasano: RBCX: -61 (-161 to +17) TUT: +2.4 (-306 to +101) Kaushal: RBCX -142.3 (-590.1 to +136.8) TUT: +32.8 (-188.0 to +170.0)
Statistical test	**Type**	Fasano: Random effects model. Kaushal: Not reported.
	p value	Fasano: All procedures, p<0.0001 Kaushal: RBCX vs. partial ME/TUT, p=0.02.
Outcome	**Name**	**Change in liver iron concentration** (mg/gm/year)
Effect size	**Value (mean range)**	Fasano: RBCX: -5.7 (-12.0 to +0.2) TUT: +1.5 (-3.7 to +9.3)
Statistical test	**Type**	Kruskal Wallis test
	p value	(All 3 procedures) p=0.0235
Outcome	**Name**	**Alloimmunisation rates** (case/100 units)
Effect size	**Value**	Fasano: RBCX: 0.50 Partial ME/TUT: 0.51 Kaushal: not reported
Statistical test	**Type**	Not reported
	p value	Fasano: RBCX versus partial ME/TUT, p=0.78 Kaushal: not reported
Comments		

Study name		**ac: Hilliard et al, 1998**
Size of study groups	**Treatment (Cobe)**	n=11
	Comparator (TUT)	n=11
Study duration	**Time unit**	Not reported
Type of analysis	**ITT/per protocol**	NA
Outcome	**Name**	**Procedure interval**

Effect size	**Value** (mean, range)	Cobe: 35.1 days (29.1–43.3) TUT: 29.6 days (21.6 – 37.7)
Outcome	**Name**	**Pre-procedure HbS**
Effect size	**Value** (mean, range)	Cobe: 43.6% (28.7 - 55.9) TUT: 37.6 % (18.8 – 57.5)
Outcome	**Name**	**Red blood cells used**
Effect size	**Value** (mean, range)	Cobe: ~230 ml/kg/year (~170 – 330) TUT: ~150 ml/kg/year (~100 – 180)
Outcome	**Name**	**Donor exposure**
Effect size	**Value** (mean, range)	Cobe: ~39 units (~30 – 51) TUT: ~30 units (~9 – 50)
Outcome	**Name**	**Ferritin/iron chelation (**Cobe Spectra system **only)**
Effect size	**Value**	2 patients with initial serum ferritin >5000 ng/ml and on chelation stabilised but did not change ferritin levels. 1 patient with initial serum ferritin <5000 ng/ml and on chelation decreased ferritin levels. 2 patients with initial serum ferritin <5000 ng/ml and not on chelation did not change ferritin levels. 1 patient not on chelation maintained ferritin levels between 50-200 ng/ml.
Outcome	**Name**	**Complications**
Effect size	**Value**	No serious procedural complications. 3/11 had occasional venous access problems. No recurrent stroke where mean pre-procedure HbS was 44%. No patients developed alloantibodies or infectious complications.
Comments		Approximate data has been abstracted from graphs in the paper. No statistical analysis was conducted.

Study name	**ad: Singer et al. 1999**			
Size of study groups	**Treatment**	Cobe Spectra system depletion/RBCX n=8		
	Control	Simple transfusion n=8		
	Analysis	Before and after study, analysis not described		
Study duration	**Time unit**	Mean 9 months (range 6-11)		
Outcome	**Unit**	**Depl/RBCX**	**Simple transfusion**	**Notes**
Duration of procedure	hours	Approx. 1.5	4-6	
Blood usage	cc/kg	22.7	12.8	Mean 77% increase
RBC used (n=8, 6	Units	155 (3.2 per	77 (1.6 per	

months)		procedure)	procedure)	
Chelation therapy	patients	5/8	5/8	
Ferritin (n=8)	ng/ml (mean)	1995	2651	NS
Ferritin (n=5 on chelation)	ng/ml (mean)	1995	2888	Mean 32.3% decrease
Transfusion iron loading	net ml RBC/kg	1.47 (range 0.5-2.5)	~9 (range 5.6-15.5)	1ml = 1 mg iron
Comments	Patients not on chelation therapy had stable iron levels. No patients experienced complications. None developed alloantibodies or infectious complications			

7.6.2 Justify the inclusion of outcomes in table B9 from any analyses other than intention-to-treat.

Most of the included studies are retrospective reviews of routinely collected clinical data. There are 15 peer-reviewed journal papers and one journal letter, with the rest being conference abstracts. Outcomes are primarily limited to those that are immediately available following the procedure. Therefore there is little distinction to be made between intention-to-treat and per-protocol analysis. No patients were described as lost to follow up and where patients have changed treatment modality this is usually as part of a before-and-after comparison.

7.7 Adverse events

In section 7.7 the sponsor is required to provide information on the adverse events experienced with the technology being evaluated in relation to the scope.

For example, post-marketing surveillance data may demonstrate that the technology shows a relative lack of adverse events commonly associated with the comparator.

7.7.1 Using the previous instructions in sections 7.1 to 7.6, provide details of the identification of studies on adverse events, study selection, study methodologies, critical appraisal and results.

The literature search used for clinical outcomes was broad and would have identified studies designed primarily to investigate safety outcomes. No additional literature search was completed for this section.

Only 4 studies were identified that were designed primarily to assess safety outcomes, or that are only included because of important safety information (Patel, Tsitsikas, Venkateswaran, Wahl). These are reported in 7.7.2, tables B10a-d. The studies included in the clinical evidence also contain adverse events and other safety information, and this is included in the study outcome Tables B9a-ad. No studies reported that they were powered to analyse adverse events.

7.7.2 Provide details of all important adverse events reported for each study. A suggested format is shown in table B10.

The safety outcomes in studies included as clinical evidence are not grouped in a table here, primarily due to the reporting differences between studies:

- Reporting adverse events per procedure or per patient
- Adverse events were grouped in different categories in each study
- The severity of an event that was described as an adverse event. This is particularly true of problems with vascular access.
- Categorising adverse outcomes associated with sickle-cell disease, e.g. stroke, as an adverse event.

Information on adverse events for each study included in the clinical evidence is presented within the report in tables B9a-u, in the context of the information for each study. Where available, any statistical analysis reported by the authors is presented in these tables; in most cases this was not reported.

Table B10a-d Adverse events across patient groups

Study Name	**a: Patel et al. 2013**	
Objective	Assess tolerability and complication rate of automated red cell exchange transfusion in patients with SCD	
Location	Homerton University Hospital, London, UK	
Design	Retrospective study, abstract only	
Duration of study	May 2011 to December 2012	
Population	Patients with SCD	
Sample size	40 patients, but only 32 with symptomatic history available 203 transfusions, but only 166 with documented history	
Adverse Events	**Automated RBCX** (n = stated in each row)	**Additional information**
No symptoms documented	28% (9/32)	Per patient
Paraesthesia due to citric reaction	6.0% (10/166)	Per procedure
Vasovagal symptoms	8.4% (14/166)	Per procedure
Rash requiring chlorphenamine	1.2% (2/166)	Per procedure
Infection	1.8% (3/166)	Per procedure
Mild bleeding	3.6% (6/166)	Per procedure
Major bleeding	2.4% (4/166)	Per procedure
New alloantibodies	2.5% (1/40) as reported.	Per patient
Patients who discontinued due to complications or non-toleration of procedure	5 patients reported: Hyperhaemolysis (1) Line related thrombosis (1) Difficult vascular access (1) Repeated vasovagal episodes (1) Dislike of procedure (1)	
Comment	Some of the numbers and percentages were inconsistently reported.	

Study Name	**b: Tsitsikas et al. 2013**
Objective	Report thrombocytopenia and coagulopathy
Location	Homerton University Hospital, London, UK
Design	Retrospective study, abstract only
Duration of study	Not stated
Population	Patients with SCD on a regular automated red cell exchange programme. Presumed patient overlap with study by Patel et al. 2013, but not stated.
Sample size	21 patients 100 transfusions (of which 90 had both pre- and post-transfusion fibrinogen levels recorded)

Adverse Events		**Automated RBCX** (n = 100)
Mean fibrinogen level reduction per transfusion (g/l)(range)		0.8 (0.1-1.8)
Fibrinogen level reduced below normal limit of 1.5 g/l		20.0% (18/90)
Fibrinogen level reduced by 1g/l or more		36.7% (33/90)
Mean platelet reduction (range)	per procedure	70% (32-89%)
	per patient	69.4% (48.8 – 83.6%)
Median platelet count (range)	pre-transfusion	367 $x10^9$/l (169-700 $x10^9$/l)
	post-transfusion	105 $x10^9$/l (35-285 $x10^9$/l)
Median platelet count, 7 patients with additional blood tests (range)	post-transfusion (n=7)	117 $x10^9$/l (64-182 $x10^9$/l)
	within 1 week (n=7)	279 $x10^9$/l (163-421 $x10^9$/l)
Comment	Platelets dropped significantly in all 100 procedures. No significant abnormalities were detected in the prothrombin or activated partial thromboplastin time. No patients had significant bleeding complications or developed purpura.	

Study Name	**c: Venkateswaran et al. 2011**			
Objective	To determine the rate of antibody formation			
Location	One centre in USA			
Design	Retrospective observational study comparing TUT and automated RBCX (Cobe)			
Duration of study	2002-2006			
Population	Children and adults with SCD receiving chronic transfusion therapy			
Sample size	n=93			
Adverse Events		**Automated RBCX (Cobe) n = 15**	**TUT n = 93**	**Additional information**
Patients developing new antibodies		0/15	23/93	
Total new antibodies		0	33	
New alloantibodies		0	15/23	
Immunisation rate / unit		0%	1.5%	
Duration of therapy		30 months (17-41 months)	not reported	
Comment	Limited red cell antigen matching conducted. The device name is not reported but the manufacturer has confirmed that the Cobe Spectra system was used for this study.			

Study Name	**Wahl et al. 2012**
Objective	To determine the rate of antibody formation
Location	One centre in USA
Design	Retrospective comparative study

Duration of study	1994 - 2010			
Population	Paediatric patients on chronic transfusions for SCD			
Sample size	45 patients			
Adverse Events		**Automated RBCX (Cobe) 48.9 % of patients (n = 22)**	**Simple transfusion 51.1 % of patients (n = 23)**	**Additional information**
Formation of new antibodies		3/22 (14%)	4/23 (17%)	
Total new antibodies		3 in 3 patients	6 in 4 patients	
Total new alloantibodies		1 in 1 patient	5 in 3 patients	
Rate of total antibody formation antibodies / 100 units blood		0.040	0.171	p=0.04
Rate of alloantibody formation antibodies / 100 units blood		0.013	0.143	p=0.03
Haemolytic reactions		0/22 (0%)	1/23 (4%)	
Comment	All patients received non-phenotype matched blood. Patients were defined as being on automated RBCX if at least 50% of the total units during their programme were transfused using this method. Poisson regression was used to compare the rates of antibody formation between the two groups.			

7.7.3 Describe all adverse events and outcomes associated with the technology in national regulatory databases such as those maintained by the MHRA and FDA (Maude).

The data had previously been analysed by Terumo BCT for Medical Device Reports (MDRs) in the date range of 1st July 2010 to 1st October 2014, and this was updated with results for 1st October 2014 to 23rd May 2015. This gave a total of 19 MDR that are for red blood cell exchange procedures, and a further 58 where the procedure is unknown, or faults were identified during maintenance, giving a total of 77. The reports are summarised below. The most common are Return Line Air Detector (RLAD) malfunction, leaks and fluid balance alarms. The RLAD has also been subject to a field safety notice and problems have been resolved. Terumo BCT estimate that there were approximately 120,000 RBCX procedures performed between July 2010 and October 2014.

Table B11 Terumo BCT collated complaints

Failure/ Complaint	**N**	**Procedure**	**Outcome**

RLAD Malfunction Possible risks due to RLAD failure include ineffective treatment, delayed procedure, or requirement for an additional procedure.	20	Not Specified (13)	Prior to patient connect, so no risk to patient. (6)
			Risk or consequence to patient is unknown. (5)
			Training run---no patient connected, so no risk to patient. (1)
			RLAD did not activate during priming, air observed in line. Prior to patient connect, so no risk to patient (1)
		Service (7)	Risk or consequence to patient is unknown. RLAD Malfunction condition may have existed prior to service. (5)
			RLAD Malfunction discovered during service, so no risk to patient. (2)
Leak	11	Not specified (10)	Tubing replaced, procedure completed.
			Prior to patient connect, so no risk to patient.
			Stopped procedure/no rinseback, repeated procedure.
			Early termination of procedure. Prevented rinseback.
			Early termination of procedure.
			Patient information not provided by customer. Assume procedure ended early.
			Patient outcome unknown
			Collect tubing disconnected. No medical intervention needed
			Centrifuge tubing leak due to inadequate solvent bond. This has been addressed (2)
		RBCX (1)	Patient outcome unknown.
Fluid Balance Alarms	9	RBCX (5)	Repeated procedure.
			Early termination of procedure (4)
		Not Specified (4)	No rinseback, repeated procedure.
			Repeated procedure.
			Patient outcome unknown
			No rinseback possible, transfusion required.
Failure to Boot	3	N/A	No patient connected, so no risk to patient.
Haematocrit target not achieved	3	RBCX (3)	Run ended manually, no rinseback. Patient required phlebotomy and saline infusion.
			Procedure completed, phlebotomy required.
			Early termination of procedure, phlebotomy required.
Tubing kink	3	Not Specified	Prior to patient connect, so no risk to patient.

Patient Death--unrelated to procedure	2	RBCX (2)	Patient Death--unrelated to procedure.
Sets failed system's diagnostic tests prior to procedure	1	Not Specified	Prior to patient connect, so no risk to patient.
Reservoir Sensor Fault	1	Not Specified	Patient outcome unknown.
Reservoir Sensor Alarms	2	Not specified	Prime not completed, fault with AIM system
		RBCX	Patient outcome unknown.
Difficulty in separating the set luer connection to patient catheter	1	Not Specified	Procedure completed. Customer eventually successful in disconnecting patient without injury.
Hall sensor and encoder in return pump malfunction alarms	1	Not Specified	Patient outcome unknown.
Cellular clumping in set during procedure	1	Not Specified	Patient outcome unknown.
Pressure Sensor Alarm	1	RBCX	Procedure was stopped and then restarted with new inlet and return lines. One unit of blood had to be discarded due to timing issues.
Missing Cassette Barcode	1	Not Specified	Prior to patient connect, so no risk to patient.
Mis-assembly	1	Not Specified	Prior to patient connect, so no risk to patient.
Return Pressure Alarm	1	Not Specified	Patient outcome unknown.
Hypervolaemia	1	Not Specified	No injury was reported regarding this incident, and based on the patient's TBV and amount of saline that was unintentionally delivered (worst case), our internal risk guideline determines that there was unlikely to be any risk for this situation.
Patient Reaction--	4	Not Specified	Patient outcome unknown. Patient discharged.

Undetermined Cause		RBCX (3)	Patient treated for hives and subsequently discharged (1)
			Patient fainted after discharge (2)
Seal Safe Malfunction	1	N/A (Seal Safe)	Device reportedly shocking nurses and cutting through tubing.
Air in access line	1	RBCX	Early termination of procedure, medical intervention via a phlebotomy
"CELLS WERE DETECTED IN PLASMA LINE FROM CENTRIFUGE" alarm	1	RBCX	Haemolysis due to patient condition. Patient subsequently died due to disease progression
Centrifuge noise	1	Not specified	Problem with disposables
Crack in tubing	1	Not specified	Treatment switched to another machine
Data input	1	Service (1)	Service engineer noted height and weight incorrect for a previous procedure. Outcome not known
"Obstacle in centrifuge" alarm	1	Not specified	Patient outcome unknown
Pump problem, unspecified	1	Not specified	No rinseback possible, transfusion required. Patient outcome unknown.
Roller clamp incorrectly assembled	1	Not specified	Prior to patient connect, so no risk to patient
Touchscreen not working	1	Not specified	Electrical cable faulty, no adverse effect on patients

MHRA was searched for relevant information; however the new format of the website makes efficient searching very difficult. One field safety notice from Terumo BCT was identified from 2012, concerning the RLADs. This issue is described in 7.7.4.

7.7.4 Provide a brief overview of the safety of the technology in relation to the scope.

Terumo BCT collects market surveillance data for the Terumo BCT Spectra Optia system and this is regularly reviewed as part of the Terumo BCT risk management process, which complies with ISO 14971:2012. In 2012 Terumo

BCT issued a Field Safety Notice to inform customers of failures with the RLAD, which is designed to prevent air from being returned to the patient. The failures can result in the Spectra Optia system not being able to prime and start a procedure, or not being able to complete a procedure without restarting with a new tubing set. In 2014, Terumo BCT issued an update to the Field Safety Notice, proposing to redesign the RLAD component and upgrade software to reduce the occurrence of false air detection. The RLAD failure safety notices were issued on the request of the US Medicines and Healthcare Products Regulatory Agency (MHRA). According to Terumo BCT risk management processes, the failure mode was related to critical mononuclear cell collection protocols (MNC) procedures being interrupted or postponed by the alarms, and not related to any of the exchange protocols (including RBCX). The failure modes were low risk.

The use of Spectra Optia for automated RBCX does not appear to be associated with an increased risk of adverse events in comparison to top-up transfusion, manual exchange or other apheresis procedures. Typical immediate events such as citrate (anticoagulant) sensitivity and vasovagal reactions are common to other apheresis or blood donation activities. Alloimmunisation rates do not appear to be different to manual exchange, despite increased donor exposure and are lower than for top-up transfusions. Issues with peripheral venous access are related to patients having a long history of transfusions. Temporary femoral central venous cannulae or indwelling dual-lumen ports may be employed depending on local practice. Note that differences in the flow rates achievable using different venous access routes may affect procedure times.

7.8 Evidence synthesis and meta-analysis

When more than one study is available and the methodology is comparable, a meta-analysis should be considered.

Section 7.8 should be read in conjunction with the 'Medical Technologies Evaluation Programme Methods Guide', available from www.nice.org.uk/mt

7.8.1 If evidence synthesis is not considered appropriate, give a rationale and provide a qualitative review. The review should summarise the overall results of the individual studies with reference to their critical appraisal.

Although most of the studies are similar designs (retrospective observational studies using routinely collected clinical data), the range of outcomes, patient characteristics (where described) and the multiple units used do not permit useful meta-analysis to be conducted. Instead we have collated the outcomes from all included studies, grouped according to Table B3.

Table B12a Collated outcomes - manual versus automated RBCX and manual only

Outcome	Measure	Manual	Auto	Sig?	Reference
Procedure duration	Mins	245 (195-360)	87.3 (75.5-126): 1st yr 91.0 (64-154): 2nd yr	Y	Dedeken
Procedure duration	Mins	Not reported	70 (Cobe)	-	Cabibbo
Procedure duration	Mins	257	115	Y	Kuo/Kuo
Procedure interval	Days	28 (14-114)	63 (19-91)	Y	Duclos
Procedure interval	Days	28 (21-29)	34 (28-35.5): 1st yr 42 (28-42): 2nd yr	Y	Dedeken
Procedure interval (prescribed)	Weeks	4.4 4 (3-4)	7.1 7.5 (4-8)	Y Y	Kuo 2012 Kuo 2015
Procedure interval (actual)	Weeks	4.86 ± 1.80	6.66 ± 1.65	Y	Kuo/Kuo
Procedure interval	Days	45-90	-	-	Cararra
Procedure interval	weeks	9.7 (4.0 – 22.1)	-	-	Webb
Procedure frequency	per year	7.1 (2.4 – 2.8)	-	-	Webb
Target achievement: HbS	Patients	All	All	-	Dedeken
Target achievement: HbS	Proportion of procedures	0.5 (0.28 – 0.90)	0.8 (0.4 – 1.0)	N	Woods
Target achievement: HbS in 2/3rds of procedures	Proportion of patients	2/21 (9.5%)	11/30 (36.7%)	Y	Kuo/Kuo
HbS	%	33.5 (25-42)	40 (28.5-42): 1st yr 46 (31-48): 2nd yr	Y	Dedeken
HbS	%	36 38	34 34	 Y	Fasano Kaushal
Pre-procedure HbS (all)	%	45.6 (20.6-81)	47.5 (22-84)	Y	Duclos
Pre-procedure HbS (procedures within 40 days)	%	44.3 (20.6-63)	32 (22-60)	Y	Duclos
Pre-procedure HbS	%	55 (16-72)	50 (27-76)	N	Kuo/Kuo
Pre-procedure HbS	%	45.9 (26- 74.2)	-	-	Webb
Pre-procedure Hct	%	27 (22-35)	25.5 (19-31.6)	Y	Duclos
Post-procedure Hct	%	0.31 (0.25-0.38)	0.31 (0.23-0.35)	N	Kuo/Kuo
Pre-procedure Hct	%	25.1 (22.2 – 28.7)	-	-	Webb

Outcome	Measure	Manual	Auto	Sig?	Reference
RBC used (n = 10)	Units	39.5 (15-79)	67.0 (49-120) – 1st yr 65.5 (38-137) – 2nd yr	Y	Dedeken
RBC used	Units	1.8	6.1 (mixed devices)	-	Cabibbo
RBC used	Units/year	32	55	Y	Kuo/Kuo
RBC used	ml/kg	18.3 (15.1-20)	32.2 (27.4-36.1): 1st yr 30.0 (26.8-36): 2nd yr	Y	Dedeken
RBC used	ml/kg/year	127	241	Y	Kuo/Kuo
Blood vol transfused (all)	ml/kg	11.1 (6.6-20)	41 (19.6-60)	Y	Duclos
Blood vol transfused (procedures within 40 days)	ml/kg	11 (6.6-20)	29 (19.6-52)	Y	Duclos
Ferritin	µg/L	666 (182-1512)	255 (52-811): 1st yr 148 (9-622): 2nd yr	Y	Dedeken
Ferritin	ng/ml	1527 (731 – 2568)	875 (578 – 2659)	N	Woods
Ferritin change	ng/ml/month	+19 (-42 to +106) +41.7 (-91.3 to +207.8)	-61 (-161 to +17) -142.3 (-590.1 to +136.8)	Y Y	Fasano Kaushal
Ferritin change	Incr / decr / same	7/7 incr	1/13incr, 7/13 decr, 5/13 same (mixed devices)	-	Cabibbo
Liver iron change	mg/gm/year	+1.6 (-9.2 to +10.9)	-5.7 (-12.0 to +0.2)	Y	Fasano
Iron chelation	Yes/no	2/10	2 patients stopped	-	Dedeken
Iron chelation	No. of pts	6/21 (28.6%)	7/30 (23.3%)	N*	Kuo/Kuo
Iron chelation	Yes/no	4/7	1/13	-	Cabibbo
Stroke rate	per 100 years	1.1	-	-	Webb
Hospital admissions	per 100 years	121	-	-	Webb
Alloimmunisation rate	Rate/100 units	0.51 1.1	0.50 0.55	N N	Fasano Kaushal
Adverse events	Per procedure	10/202	11/199	N	Kuo 2015
Procedures converted to top-up	Count	0/202	11/199	Y	Kuo/Kuo
Catheter complications	Number	1/17	15/21	Y	Woods

* Kuo 2012: RBCX was better than ME at maintaining a near zero iron balance due to considerable variability in the manual group

Table B12b Collated outcomes - Spectra Optia system single arm (including depl/RBCX vs. RBCX and Cobe Spectra system / Spectra Optia system)

Outcome	Measure	Spectra Optia system	Reference
Procedure duration	mins	Depl/RBCX: 148±51 vs. RBCX: 147±43	Kuo
Procedure duration	mins	90 ± 22 (No difference for depl/RBCX vs. RBCX) Children: 81±16 vs. adults: 95±24	Quirolo/Quirolo
Procedure duration	hours	2-3	Asma
Procedure interval	weeks	5 (4-8)	Kuo
Target achievement: FCR	Proportion	0.90 ± 0.17 (No difference for depl/RBCX vs. RBCX)	Quirolo/Quirolo
Target achievement: Hct	% difference	1.03 ± 0.07	Quirolo/Quirolo
Pre-procedure HbS	%	40.37 (28.8 – 55.0)	Baker
Pre-procedure HbS	Count	1/7 patients – higher in depl/RBCX	Kuo
Pre-procedure HbS	%	74.5 ± 13.3% (40.8 – 99.0)	Asma
Pre-procedure HbS	%	37.97 ± 12.81 (No difference for depl/RBCX vs. RBCX)	Quirolo/Quirolo
Post-procedure HbS	%	10.9 (4-30)	Baker
Post-procedure HbS	%	13.88 ± 6.03 (No difference for depl/RBCX vs. RBCX)	Quirolo/Quirolo
Post-procedure HbS	%	24.6 ± 10.1% (8.3 – 69.5)	Asma
Pre-procedure Hct	L/L	0.269 (0.22 – 0.343)	Baker
Post-procedure Hct	L/L	0.274 (0.23 – 0.34)	Baker
Post-procedure Hct	Count	2/7 patients: lower in depl/RBCX	Kuo
Post-procedure Hct	%	Overall: 31.4 ± 2.7 RBCX: 30.8±2.6 vs. depl/RBCX: 32.9±2.2	Quirolo/Quirolo
Pre-procedure Hct	%	24.2 ± 3.5 (15.0 – 31.0)	Asma
Post-procedure Hct	%	27.5 ± 1.1 (26.0 – 31.0)	Asma
RBC used	ml	1895 ± 670 RBCX: 2016±729 vs. depl/RBCX: 1562±281* Children: 1449±260 vs. adults: 2118±702	Quirolo/Quirolo
RBC used	ml/kg	15.4 ± 5.1 (No differences)	Quirolo/Quirolo
RBC used	units	10.5	Todd
RBC used	units	8 units (5-10.5)	Sturgeon
RBC used	units	6.2 ± 0.6 (5.0 – 7.0)	Asma
RBC reduction with depl/RBCX	ml	134 (98-502) 3/16 (18.8%) saved >1 unit	Quirolo/Quirolo
RBC reduction with depl/RBCX	ml/kg/year	25	Kuo

Outcome	Measure	Spectra Optia system	Reference
RBC reduction with depl/RBCX	units	2	Trompeter
Replacement volume	ml	1893.9 ± 231.8 (1276 – 2482)	Asma
Blood volume processed	ml	5029.3 ± 543.8 (3693 – 6477)	Asma
Blood volumes processed		0.8 ± 0.2	Quirolo/Quirolo
Liver iron (at baseline/ 12/18/24/36 mths), patients on chelation	mg/m	13.9 / 8.5 / 4.8 / 6.6 / 4.7	Todd
Liver iron (at baseline/ 12/18/24/36 mths), patients not on chelation	mg/m	1.8 / 1.4 / 1.4 / 2.2 / 1.5	Todd
Liver iron change (36 mths)	%	-66	Todd
Ferritin	-	Same	Kuo
Ferritin change	µg/l	Pre: 2523 ± 3198 µg/l (11-15990) Post: 2659 ± 3229 µg/l (21-14229)	Sturgeon
Iron chelation	-	0/7 patients	Kuo
Change in hospital admissions (when interval ≤8 weeks)	days per year	pre: 34.8 ± 71.4 (0-365) post: 7.60 ± 9.87 (0-34) p<0.005	Sturgeon
Change in hospital admissions (infrequent procedures)	days per year	pre: 11.64 ± 15.33 (0-43) post: 42.26 ± 66.75 (3-190) p=0.161	Sturgeon
Adverse events	Patients	13/72	Quirolo/Quirolo
Maternal complications	Count	3/24 (12.5%)	Asma
Foetal complications	Count	1/24 (4.2%)	Asma
Maternal death	Count	0/24 (0%)	Asma
Adverse events	Count	4/45 procedures	Asma
Alloimmunisation	Count	4/24 patients	Asma

Table B12c Collated outcomes - Cobe Spectra system single arm (including depl/RBCX vs. RBCX)

Outcome	Measure	Cobe Spectra System	Reference
Procedure duration	Hours	2.0 ± 0.7	Shrestha

Procedure duration	Minutes	Depl/RBCX: 103.9 ± 12.4 RBCX: 107.3 ± 6.7	Sarode
Procedure interval	weeks	8	Billard
Procedure interval	weeks	5.2 (4-6) (1 pregnancy: 3)	Kalff
Procedures/year	Count	2.6 (1.1 – 4)	Masera
Procedure interval	days	Depl/RBCX: 52.9 ± 6.5 (median 52.7, range 44.6-74.5) RBCX: 37 ± 7.0	Sarode
Procedures/patient/year	Number	Depl/RBCX: 7.0 RBCX: 9.3	Sarode
Pre-procedure HbS	%	39.3 (median 38.2, range 35-50)	Billard
Post-procedure HbS	%	6.5 (median 6.5, range 3-12)	Billard
Pre-procedure HbS	%	47.4 (40.7 – 59.3)	Kalff
Post-procedure HbS	%	n=13: 25.5 (18.5 – 32.6) n=7: 25.0 (18.5 – 32.6)	Kalff
Pre-procedure HbS	%	63 (49-83	Masera
Post-procedure HbS	%	20 (7-34)	Masera
Pre-procedure HbS	%	41.8 ± 6.1 (median 43.0, range 30.6 – 52.4)	Sarode
Post-procedure HbS	%	9.8 ± 2.4 (median 9.9, range 6.7 – 16.4)	Sarode
Pre-procedure Hct	%	27.8 ± 2.4 (median 28.0, 23.0-33.2)	Sarode
Post-procedure Hct	%	32.8 ± 1.6 (median 32.9, range 30.4 – 36.6)	Sarode
RBC used	ml/kg	332 (range 280-370) per year 55 (range 47-62) per procedure	Billard
RBC used	units	5.7	Kalff
RBC used	ml/kg	~30 per procedure	Masera
RBC used	Units	6.3 ± 1.7	Shrestha
RBC used	Units	8.4	Sarode
RBC used	ml/kg	Depl/RBCX: 35.5±4.1 (median = 36.0) RBCX: 39.5±4.6 (median 40.4)	Sarode
RBC saved by depletion*	ml/kg	2.9 (median 2.0, range 0.9 - 9.0)	Ma
Ferritin change	ng/ml	Start: 2977 (median 1933) End: 2885 (median 1922)	Sarode
Ferritin change	ng/ml	Start: 408 (median 280, range 22-1476) End: 429 (median 294, range12-2220) (p=0.267)	Billard

Ferritin change (low)	µg/l	Pre-RBCX: <300 RBCX: <600	Kalff
Ferritin change (med)	µg/l	Pre-RBCX: 465 (311-582) RBCX: 282 (69-361)	Kalff
Ferritin change (high)	µg/l	Pre-RBCX: 2700-10700 RBCX: 900-7700	Kalff
Ferritin change	ng/ml	Pre-RBCX: 1175 (45-2648) RBCX: 915 (270-1866)	Masera
Ferritin reduction	Not reported	730 ± 421 (median 575, 209 – 1277)	Willis
Ferritin (end of therapy)	Not reported	1494 ± 722 (median 722, 12 – 3808)	Willis
Iron chelation	Count	1/13 discontinued 3/13 began	Masera
Iron chelation	Yes/no	3 No, 15 Yes, 2 discontinued	Sarode
Iron chelation	Yes	4/5	Willis
Target achievement: Hct	Success rate, %	87	Shrestha
Target achievement: HbS	Success rate, %	95	Shrestha
Target achievement, HbS	Success rate, %	95 (55/58)	Ma
Hospital admissions	Count	Pre-RBCX: 60 RBCX: 13	Kalff
Hospital admissions	Rate/person	Pre-RBCX: 9 (2-16) RBCX: 0.5 (0-6)	Kalff
Hospital admissions	Events/year	Pre-RBCX: 1.9 (0.4 – 3.2) RBCX: 0.2 (0 – 0.85)	Kalff
Hospital admissions	Events/year	Pre-RBCX: 1.7 (0.2-4) RBCX: 0.69 (0-1.8) RBCX + HU: 0.24 (0-1)	Masera
Hospital admissions (pain crises)	Events/year	Pre-RBCX: 4.8 (0.2-12) RBCX: not reported RBCX + HU: 1.79 (0-5.5)	Masera
Adverse events (overall)*	%	18.5 (109/594)	Sarode
Adverse events (overall)	%	13.5 (15/112)	Sarode

Table B12d Collated outcomes - Spectra Optia system versus Cobe Spectra system

Outcome	Measure	Spectra Optia system	Cobe Spectra System	Significant	Reference
Procedure duration	Mins	101 ± 28	99 ± 24	N	Perseghin/ Perseghin
Procedure duration	mins	94.3 ± 17	100.2 ± 22	N	Poullin
Procedure duration	Mins	99 ± 26.32	114 ± 31.48	N	Turhan

Pre-procedure HbS	HbS%	60% ± 16%	63% ± 12%	N	Perseghin/ Perseghin
Pre-procedure HbS	HbS%	73.44 ± 20.05	73.96 ± 19.98	N	Turhan
Pre-procedure HbS	HbS%	51.2 ± 11	51.1 ± 10	N	Poullin
Post-procedure HbS	HbS%	23% ± 7%	20% ± 5%	N	Perseghin/ Perseghin
Post-procedure HbS	HbS%	23.6 ± 14.10	22.43 ± 13.48	N	Turhan
Post-procedure HbS	HbS%	19 ± 5	18.8 ± 5	N	Poullin
HbS change	%	-68.65 ± 17.23	-73.96 ± 22.43	N	Turhan
Pre-procedure Hct	%	24.54 ± 8.89	24.18 ± 4.17	N	Turhan
Hct target	%	27.34 ± 2.33	26.9 ± 1.99	N	Turhan
Post-procedure Hct	%	28.11 ± 4.21	27.53 ± 3.2	N	Turhan
Hct	%	29.9 ± 4	28.8 ± 3	N	Poullin
FCR	%	38.3 ± 7	37.9 ± 7	N	Poullin
FCR	%	28.86 ± 6.09	25.74 ± 7.63	N	Turhan
RBC used	ml	1817 ± 270	1746 ± 271	Y	Poullin
RBC used	Units	6.2 ± 2.4	6.6 ± 1.5	N	Perseghin/ Perseghin
RBC used	Units	6.1 ± 1	6.1 ± 1	N	Poullin
RBC used	Units	6.67 ± 2.25	6.72 ± 2.55	N	Turhan
RBC volumes exchanged	Units	1.31 ± 0.38	1.51 ± 0.44	N	Turhan
Blood volume processed	ml	4126 ± 795	4298 ± 787	N	Poullin
Blood volume processed	ml	4440 ± 1639	4836 ± 1999	Y	Turhan
Target achievement: Hct	% of target	101% ± 4%	100% ± 8%	N	Perseghin/ Perseghin
Adverse Events (grade 3)	Count	3/159	0/188	N	Turhan
PLT reduction	%	53.52 ± 13.80	51.83 ± 20.44	N	Turhan

Table B12f Collated outcomes – automated RBCX versus top-up transfusions

Outcome	Measure	Auto RBCX	TUT	Significant	Reference
Procedure duration	Hours	~1.5	4-6	-	Singer
Procedure interval	Days	35.1 (range 29.1 – 43.3)	29.6 days (21.6 – 37.7)	-	Hilliard
Pre-procedure HbS	%	43.6 (range 28.7 – 55.9)	37.6 % (18.8 – 57.5)	-	Hilliard
Donor exposure	units	~39 (range 30-51)	~30 units (~9 – 50)	-	Hilliard

RBC used	units/year	Group 1: 61 Group 2: 54 Group 3: 43	Group 1: 34 Group 2: 28 Group 3: NA	-	Adams
RBC used	ml/kg/year	~230 (range 170–330)	~150 ml/kg/year (range ~100 – 180)	-	Hilliard
RBC used	cc/kg	22.7	12.8	-	Singer
RBC used	units/6 months	155	77	-	Singer
RBC used	units	3.2	1.6	-	Singer
HbS	%	34%	33%		Fasano/ Kaushal
Ferritin	ng/ml	Group 1: 567-2857 Group 2: 1870-7623 Group 3: 416-931	Group 1: 2247-7373 Group 2: 1465-7640 Group 3: 446- 906	-	Adams
Ferritin (all)	ng/ml	1995	2651	-	Singer
Ferritin (patients on chelation)	ng/ml	1995	2888	-	Singer
Ferritin change	ng/ml/month	-61 (-161 to +17)	+2.4 (-306 to +101)	Y	Fasano/ Kaushal
Liver iron change	mg/gm/year	-5.7 (-12.0 to +0.2)	+1.5 (-3.7 to +9.3)	Y	Fasano/ Kaushal
Transfusion iron loading	net ml RBC/kg	1.47 (range 0.5-2.5)	~9 (range 5.6-15.5)	-	Singer
Chelation	Count	Group 1: 1/3 discontinues	-	-	Adams
Alloimmunisation	Rate/100 units	0.50	0.51	N	Fasano/ Kaushal

7.9 Interpretation of clinical evidence

7.9.1 Provide a statement of principal findings from the clinical evidence highlighting the clinical benefit and any risks relating to adverse events from the technology.

Procedure duration: Procedure duration is substantially reduced by using automated rather than manual exchange. Data is lacking for manual exchange but is reported in Dedeken and Kuo/Kuo as 245 and 257 minutes,

or just over 4 hours, with a maximum of 6 hours. In comparative studies, automated exchange requires an average duration of between 70-115 minutes, or around 1-2 hours, with a maximum of 2.5 hours. Data from single arm studies support this, indicating average durations of around 1.5-2 hours and maximum of around 3 hours. King College Hospital patient information leaflet indicates that emergency manual exchange can take up to 8 hours whereas planned automated RBCX (using Spectra Optia system) usually takes 1-4 hours.

Procedure interval: In comparative studies, the mean procedure interval for manual exchange ranged from 4-5 weeks whereas for automated exchange this was around 5-9 weeks. Single arm studies using the Cobe Spectra system or Spectra Optia system support this difference, with mean procedure intervals between 5 and 8 weeks. This means in comparative studies the mean number of procedures per year is reduced from a range of 11-13 for manual to around 6-11 for automated. Single arm studies using manual exchange report longer intervals than in the comparative studies; 45-90 days in Cararra and 9.7 (4-22) weeks in Webb. In Cararra the long term HbS target was relatively high at 60-70% , compared to <30% or <50% for most other studies. The mean HbS% in Webb was 45.9% with 5/15 patients maintaining a value of >50%, but this is not dissimilar to other studies.

Abnormal haemoglobin (HbS%): The target for regular exchange procedures is usually to maintain HbS at below 30% or 50% depending on the indication. Pre-procedure HbS can be used as a measure of chronic HbS levels. Not every study distinguished between pre and post-procedure HbS. In 2 comparative studies HbS was slightly but significantly higher with automated RBCX than in manual (Dedeken, Duclos), in 1 study the values were higher for manual (Fasano/Kaushal) and in 1 they were not statistically different (Kuo/Kuo). Pre-procedure values varied greatly across single arm studies using automated exchange (from around 30-80%). This wide variation may reflect differences in patient populations or local practice and obscures whether automated RBCX has any advantage or disadvantage for this outcome.

It is not generally reported *how* the procedure interval was determined. Were intervals chosen based on the last pre-procedure HbS% measure, using a standard value or based on regular measurements taken in the weeks following treatment?

Post-procedure HbS was not reported in any of the studies comparing manual and automated RBCX. Achievement of target HbS was reported in 3 studies. In 1 of these studies 36.7% of patients receiving automated RBCX achieved their post-procedure HbS target in at least 2/3^{rds} of their procedures compared to 9.5% receiving manual exchange (Kuo/Kuo). In Woods (2014) the proportion of patients achieving their target HbS was non-significantly higher for automated RBCX and in Dedeken (2014) all patients in both study arms achieved their target. In single arm automated RBCX studies post-procedure HbS levels have been reduced to below 10% in some patients. However, post-procedure HbS will depend on the local practice for determining target values and the indication for which the patient is being treated.

RBC volume used: It is known that automated exchange uses a larger volume of RBC units than manual exchange. The comparative studies identified here are measured in a variety of ways (units, ml, ml/kg, ml/kg/year) making aggregation difficult. However, values for automated RBCX are consistently and significantly almost twice those for manual exchange. In single arm studies the number of units per procedure is around 5-8 units, with volumes being smaller for children than for adults (Quirolo/Quirolo). The volume of packed RBC required for the automated exchange can be reduced by the addition of a depletion phase before the exchange (depletion/exchange or isovolemic haemodilution, IHD). In some patients this reduction can be 1-2 units for a procedure that takes the same amount of time and produces the same reduction in HbS%. However, this protocol modification is not suitable for all patients as the haematocrit is initially reduced by venesection and replacement fluid. Therefore minimum pre-procedure haematocrit values are used to determine which patients this procedure is appropriate for.

Haematocrit: In general post-procedure haematocrit is slightly higher than pre-procedure haematocrit. A post-procedure value of around 30% is the target to

ensure hyperviscosity is avoided. Only Duclos (2013) compared haematocrit between manual and automated exchange procedures. Pre-procedure haematocrit was slightly but significantly lower in patients treated with automatic RBCX whereas post-procedure values were not different.

Ferritin and iron chelation: The use of regular top-up transfusion is known to cause iron overload in the long term. The purpose of red blood cell exchange procedures is to achieve reductions in HbS% whilst minimising positive iron balance. In comparative studies ferritin levels were either higher with manual exchange compared to automated exchange, or tended to increase compared to decreasing/remaining stable. This difference between the modalities was not always statistically significant, but the direction of the difference was consistent across studies. Automated exchange was superior to manual exchange.

However, patients had a wide range of values for ferritin and the use of chelation therapy was mixed in the patient populations. Also, compliance with chelation therapy may be poor in some patients in these studies. In general the single arm studies support the suggestion that the use of automated exchange can prevent the accumulation of iron (serum ferritin and liver iron) where this has not already occurred and at least stabilise values where it has. Sturgeon (2009) showed a negative correlation between change in serum ferritin with regular automated RBCX and steady state haemoglobin concentration (µg/ml). In some patients iron levels can be reduced over time such that chelation therapy can be discontinued. Two patients in Cabibbo (2005), 1 in Masera (2007), 1 in Adams (1996) and 2 in Sarode (2011) were able to discontinue chelation therapy following use of automated RBCX. However, 3 patients in Masera (2007) were required to begin chelation therapy following between 4-10 years of automated RBCX. However thresholds for the use of chelation therapy may vary and the decision to reduce or discontinue this medication may depend on other factors.

Hospital admissions and complications of sickle cell disease: No comparative studies looked at the effect of automated versus manual RBCX on hospital admissions or SCD complications. Three single arm automated RBCX studies

reported reductions in hospital admissions before-and-after automated RBCX treatments. Sturgeon (2009) reported that this only occurred for patients receiving frequent automated RBCX procedures (at least every 8 weeks): from a mean of 34.8 days per year (before treatment) to 7.60 days per year. Similarly Kalff (2010) and Masera (2007) reported apparently substantial reductions in admission rates, although these were not statistically tested. In a single arm study using manual exchange Webb (2014) reported 1.1 strokes per 100 patient years and 121 hospital admissions per 100 patient years. This appears to be slightly higher than in the single arm automated RBCX studies, but it is difficult to draw conclusions from non-comparative studies.

Bavle/Bavle was the only study that reported growth rate in children. The numerical data is difficult to interpret but the conclusion was that automated RBCX improved the growth of children compared to their growth before treatment and compared to other children with SCD. However, it is not reported in this study what therapies the comparison group may have received.

Comparison between top-up transfusion and automated RBCX

There is limited data in this comparison. Three of the four studies in this group were before-and-after intrapatient comparisons. As expected RBC use was much higher in automated RBCX, being about twice that for top-up transfusions. Singer (1999) reported that procedure duration was substantially shorter for automated RBCX and Hilliard (1998) reported that procedure interval was longer, but statistical testing was not conducted. As with manual exchange there was significant variation in the ferritin and liver iron values. There was a consistent trend in all three studies that reported these outcomes for iron level to either reduce or remain stable using automated RBCX. This was only statistically tested in Fasano/Kaushal where the difference was significant. Singer reported that despite a higher RBC usage in automated RBCX, TUT produced a higher net gain of iron during transfusion. Similarly, Fasano/Kaushal reported no difference in the rate of alloimmunisation between the two therapies.

7.9.2 Provide a summary of the strengths and limitations of the clinical-evidence base of the technology.

The evidence base comparing manual and automated red blood cell exchange using Cobe Spectra system or Spectra Optia system is limited in both quality and quantity. This evidence base has been supplemented by including single arm studies. Further studies were identified during the literature search that evaluated the use of these technologies in treating sickle cell crises or in mixed emergency and prophylactic indications, but these were excluded as outside the scope of the evaluation.

In general, most studies conducted retrospective reviews using routine clinical data and this suggests a low risk of performance and assessment bias. This also indicates that the results reported are likely to be realisable in general practice. However, patient selection was poorly described in almost all reports so that there is a high risk of selection bias ('cherry-picking'). Taking this into account we can use the reported data to represent 'best-case' scenarios which still has value in determining the technology patient and system benefits.

A significant proportion of the studies are reported in conference abstracts and in unstructured, non-peer-reviewed journal papers. Reporting is generally poor and in some cases the data is presented in a confusing manner. The heterogeneity of patient populations, comparative study designs and outcome measures makes it difficult to reach substantive numerical conclusions for many outcomes.

7.9.3 Provide a brief statement on the relevance of the evidence base to the scope. This should focus on the claimed patient- and system-benefits described in the scope.

Only four studies were identified that directly compared automated red blood cell exchange using the Spectra Optia system with manual exchange. We believe that the Cobe Spectra system should be treated as equivalent to the Spectra Optia system for the purposes of this evaluation, given the similarity in all relevant clinical and procedural outcomes reported. Several outcomes

identified in the scope were not addressed by any of the studies in this review. These include: staff time, BMI and growth in children, clinical complications of sickle cell disease and quality of life.

Regarding the claimed benefits:

- The evidence support the claim that procedure interval is longer with automated RBCX than with manual exchange. The difference is slightly smaller than that claimed in the scope being around 4-5 weeks for manual and 6-7 weeks for automated.

- The evidence supports the claim that exchange procedures are quicker using Spectra Optia system/ Cobe Spectra system than manual. Absolute values vary significantly but manual procedures take around 4-6 hours versus 1.5-2.5 hours for automated. Both durations are slightly shorter than those claimed in the scope.

- The evidence supports the claim that a small number of patients receiving automated RBCX are able to discontinue iron chelation therapy. Serum ferritin and liver iron do not increase due to regular automated RBCX and may decrease significantly in some patients. Further, the evidence suggests that automated RBCX is superior to manual exchange in this regard.

- There is no comparative data regarding patient compliance with treatment regimes or complications of SCD.

- The evidence supports the claim that automated RBCX maintains low haematocrit levels. Although the data comparing the values with manual exchange is minimal this suggests equivalence in this parameter.

- Given that procedure time is reduced we accept the claim that patients will have a shorter hospital stay per procedure. We have no data regarding the amount of staff time required per patient for either manual or Spectra Optia system procedures. However, it seems likely

that an automated and continuous flow procedure using purpose-designed software should be quicker and less labour intensive than repeated cycles of manually conducted venesection and transfusion.

- The evidence supports a reduction in hospital admissions following the initiation of a regular and frequent regime of automated RBCX. However, this is not in comparison to manual exchange and may be considered a comparison with 'no therapy'. There is no information about the reasons for admission. There is therefore no data to support the claim that automated RBCX with Spectra Optia system reduces complications of sickle cell disease over and above any benefit obtained from top-up transfusion or manual exchange.

- The evidence supports the claim that the depletion/exchange (or isovolemic haemodilution RBCX) protocol reduces the volume of replacement RBC required in comparison to that for standard automated RBCX, using both Cobe Spectra system and Spectra Optia system devices. In many cases this reduction will not be sufficient to reduce the number of whole units of RBCs and any remaining part units will be waste. However, this reduction does represent a realisable saving in resource and cost to the NHS and a patient benefit in a reduction of total donor exposure.

- The evidence supports the claim that automated RBCX can either reduce or stabilise the accumulation of iron in comparison to top-up transfusion.

7.9.4 Identify any factors that may influence the external validity of study results to patients in routine clinical practice.

As noted above, the use of routine clinical data in many of the included studies indicates that the results reported are likely to be realisable in general practice. Four of the studies were conducted in NHS hospitals in London (Kuo/Kuo, Sturgeon, Todd, Trompeter) indicating the relevance to NHS practice. We have no reason to expect that the patient populations in the

included studies differ from real-world NHS patients, although there is a risk of selection bias indicating that reported outcomes may be best-case scenarios.

Several NHS hospitals provide patient information and protocols or guidelines available online that further support some of the claims in the scope:

- Guy's and St Thomas' (Spectra Optia system): automated exchange takes between 1-4 hours and should be repeated every 4-14 weeks. Manual exchange is longer and takes all day to complete. "This is an old-fashioned way of doing an exchange blood transfusion: the results are not as good at reducing the amount of sickle cell haemoglobin in your body as using the blood exchange machine." Note that this hospital currently requires femoral lines to be used for automated exchange, but a peripheral access service is being set up. (Guy's and St Thomas' NHS Foundation Trust, 2015)

- Kings College Hospital (Spectra Optia system): manual exchange can take up to 8 hours, automated exchange usually take 1-4 hours. (King's College Hospital NHS Foundation Trust, 2013)

- Nottingham University Hospital: "Modern cell separators e.g. Cobe Spectra system can perform automated red cell exchange. This method, if available, is preferred to manual exchange – it is quicker and allows greater control of circulating volume." (Stokley, 2011)

- University Hospital Leicester (Spectra Optia system): Manual exchange "is time-consuming and it may not be possible to achieve the desired reduction in HbS% in one procedure. It is usual that 3-4 exchanges will be necessary lasting 2-4 hours each. Modern cell separators e.g. Cobe Spectra system can perform automated red cell exchange. This method, if available, is preferred to manual exchange – it is quicker and allows greater control of circulating volume. Access to automated red cell exchange will depend on the time of day and the availability of trained staff to operate the cell separator machine." (Qureshi, 2010))

- University College Hospital (Spectra Optia system): “Some advantages over manual exchange are that the period between exchanges can be longer and there is no iron loading. Currently this can only be offered to people aged 16 and above, although there are plans to develop a service to offer this to children also.” (University College London Hospitals NHS Foundation Trust)

7.9.5 Based on external validity factors identified in 7.9.4 describe any criteria that would be used in clinical practice to select patients for whom the technology would be suitable.

The technology is suitable for the same patient group as is currently indicated for regular manual exchange. These vary between centres but include primary stroke prevention (high risk patients, determined by transcranial Doppler scan), secondary stroke prevention, severe disease (high incidence of crises), pregnancy, leg ulcers. Peripheral venous access can be an issue in patients with a long history of transfusions. Some centres require femoral central lines or dual-lumen access ports for the use of an automated device. This may place a restriction on which patients are able to receive automated RBCX.

Section C – Economic evidence

Section C requires sponsors to present economic evidence for their technology.

All statements should be evidence-based and directly relevant to the decision problem.

The approach to the de novo cost analysis expected to be appropriate for most technologies is cost-consequence analysis. Sponsors should read section 7 of the Medical Technologies Evaluation Programme Methods guide on cost-consequences analysis, available from www.nice.org.uk/mt

Sponsors are requested to submit section C with the full submission. For details on timelines, see the NICE document 'Guide to the Medical Technologies Evaluation Programme process', available from www.nice.org.uk/mt

8 Existing economic evaluations

8.1 Identification of studies

8.1.1 Describe the strategies used to retrieve relevant health economics studies from the published literature and to identify all unpublished data. The search strategy used should be provided as in section 10, appendix 3.

No additional literature search strategy was conducted for health economic studies. We considered that our clinical evidence search strategies should have identified any appropriate published economic analyses. The manufacturer provided two business cases from NHS hospitals that proposed the purchase of Spectra Optia systems and the setting up of automated RBCX services. The manufacturer also provided a copy their own costing model, written in Excel.

8.1.2 Describe the inclusion and exclusion criteria used to select studies from the published and unpublished literature. Suggested headings

are listed in the table below. Other headings should be used if necessary.

The same inclusion and exclusion criteria were used as for the clinical evidence. None of the studies identified by our literature search strategy were primarily an economic evaluation. Several of the studies included in the clinical evidence also provided a brief cost analysis, and these have been collated here.

Table C1 Selection criteria used for health economic studies – not used, see Table B1

8.1.3 Report the numbers of published studies included and excluded at each stage in an appropriate format.

See Figure 1 and Figure 2 (sections 7.2.1 and 7.2.2). Seven of the 33 studies identified by the two clinical evidence searches contained some degree of cost analysis of the intervention (automated RBCX) and/or two comparators (manual RBCX or TUT).

8.2 Description of identified studies

8.2.1 Provide a brief review of each study, stating the methods, results and relevance to the scope. A suggested format is provided in table C2.

As these are primarily brief, ad hoc analyses that are supplementary to retrospective observational studies, there was generally little detail reported about methodology or identification of resources, and no sensitivity analysis was conducted. We have therefore altered the layout of the suggested tables C2 and C3 and included the critical appraisal alongside the description and results. We do not consider these analyses to be robust or thorough, or appropriate to provide a validation check on the de novo model.

Table C2 Summary list of all evaluations involving costs

Adams (1996)	USA			
Design and Comparators	Retrospective observational before-and-after intrapatient comparison of automated RBCX (Cobe) versus TUT, patients were grouped according to their use of chelation therapy.			
Population	Children requiring chronic RBCX, n = 8: chelation therapy, n = 3; no chelation due to non-compliance, n = 4; no chelation due to no iron overload, n = 3			
Costs per year		Chelation (n = 3)	No Chelation (n = 4)	No Chelation (no overload, n = 3)
	i automated RBCX =	$21,995	$20,226	$17,553
	c TUT =	$10,492	$9,175	
Other outcomes	RBC used, ferritin, alloimmunisation			
Results	Automated RBCX is almost twice the cost of TUT, although the addition of chelation therapy costs to TUT ensure that automated RBCX is cheaper			
Resources included	Clinic fee, equipment (filter, tubing, catheters), blood bank (type and cross match, processing), apheresis fee			
Assumptions	Annual costs are calculated for each patient individually. Automated RBCX is $901/procedure.			
Critical appraisal	Although chelation therapy is mentioned in the cost analysis description the authors do not appear to have included this in the actual analysis. The authors state that deferoxamine costs between $20,000-$40,000 per year. When added to the cost of TUT this ensures that TUT is more expensive than automated RBCX. This assumes that chelation therapy is only required during TUT. Costs for resources (other than for an automated RBCX procedure) are not reported. The 3 patients in the third group (no iron overload) had only received 6-9 months of automated RBCX treatment and annual costs for these patients are projected. It is unclear what is included in the 'clinic fee' for TUT and the apheresis fee, for example staff time. This is a simplistic and hypothetical cost comparison and little detail is reported.			

Carrara (2010)	Italy	
Design and Comparators	Clinical data is only reported for manual RBCX, however the authors present a calculated cost comparison between simple transfusion, manual RBCX and automated RBCX	
Population	Hypothetical 55-kg patient with SCD (clinical data is a retrospective observational study of patients receiving manual RBCX who are resistant to hydroxyurea, n = 7)	
Costs per year (i = intervention;	i automated RBCX =	€8,476.48
	c manual RBCX =	€3,054.72

c – comparator)	c TUT = €8849
Other outcomes	Procedure interval, ferritin, iron chelation, HbS, hospital admission
Results	Automated RBCX is significantly more expensive than manual RBCX (no statistical test reported) RBC costs are the same for TUT and automated RBCX. Consumable and RBC costs are higher for automated RBCX than for manual RBCX.
Resources included	RBC, iron chelation, consumables (saline, needles, transfusion bags, apheresis kit, calcium gluconate)
Assumptions	Auto RBCX: 6 x RBC per procedure, 4 procedures/year Manual RBCX: 2 x RBC per procedure, 4 procedures/year TUT: 2 x RBC per procedure, 12 procedures/year, iron chelation (40 mg/kg, 5 days/week) Unit costs: RBC = €249/unit, apheresis kit = €625, saline = €0.9, needles = €0.52, quadruple transfusion bag = €6.4, single transfusion bag €3.3
Critical appraisal	Costs are provide for individual resources and broken down into subtotals for RBC, iron chelation and consumables. No details were provided about the source of the resource use data given that clinical data is only reported for manual exchange. Costs are those used by local health authorities and are tax free. The hypothetical apheresis device is not named. No costs are reported for staff time, blood tests, SCD-related hospital admissions, adverse events. No costs are reported for iron load tests (various methods) or cardiac function tests although these are mentioned in the main analysis. This may be due to no difference in frequency of testing between the comparison arms. The assumed frequency for manual RBCX is 6 procedures per year which is consistent with that reported from the retrospective data analysis (4-8 procedures/year). One of 7 patients included in the main data analysis required iron chelation on manual RBCX due to iron overload from previous TUT. However, the cost comparison assumes that iron chelation is only required in TUT. The model therefore appears to assume that patients on manual and automated RBCX receive this treatment before becoming iron overloaded. This is a simplistic cost comparison with little detail is reported.

Dedeken (2014)	Belgium
Design and Comparators	Before-and-after, auto RBCX with Optia (i) vs. manual RBCX (c) Evaluate the change of the costs related to transfusion and chelation over time
Population	Older children with SCD previously treated with manual RBCX, n = 10
Costs per year (i = intervention; c – comparator)	i year 1 = €132,937 i year 2 = €102,965 c final year = €107,560

Other outcomes	Procedure duration, procedure interval, RBC used, iron chelation, HbS%, ferritin, adverse events
Results	Automated RBCX was significantly more expensive than manual RBCX for the first year ($p<0.01$, Friedman test), but similar in the 2nd year
Resources included	RBCs, 1-day care facility, apheresis kit, iron chelation. For patients with <2years of automated RBCX costs for the 2nd year were extrapolated using data from the previous 6 months.
Critical appraisal	No details were provided about the source of the resource use data or the costs used. Data for manual RBCX was only collected for 6 months prior to the change to automated, so we assume that this has also been extrapolated. Staff costs are not mentioned explicitly but may be included in the '1-day facility' costs. Data on adverse events were reported but it is not clear which type of RBCX they apply to and it is not reported whether costs for these are included. No costs are explicitly included for blood tests and no data is reported for SCD-related hospital admissions. It is not reported whether costs were adjusted for inflation over the three years of the analysis or whether costs were calculated at a single time point. Costs are assumed to be for the cohort of 10 patients. In the second year of automated RBCX the procedure interval increased compared to the first year and HbS also increased. The 2/10 patients who were taking chelation therapy ceased after 1 and 10 automated procedures. The authors attribute the increased initial costs of automated RBCX to the greater used of RBC and the later reduction to the cessation of chelation therapy. This suggests that it required 2 patients to cease chelation therapy in order to offset the increased costs of RBCs with automated RBCX as 1 patient ceased after only 1 automated RBCX treatment. This is a simplistic cost summary and little detail is reported in this conference abstract. No breakdown of resources and costs is provided and variation between patients is obscured by the use of a cohort total.

Hilliard (1998)	USA
Design and Comparators	Prospective observational before-and-after intrapatient comparison
Population	Teens and adults with SCA and a history of stroke, transferred from TUT to automated RCBX (Cobe Spectra)
Costs per year	i automated RBCX = $36,085 c TUT = $26,058
Other outcomes	RBC, complications, ferritin, donor exposure
Results	Automated RBCX is more expensive than TUT unless the cost of chelation therapy is added to the cost of TUT.
Resources included	Not reported
Assumptions	i automated RBCX: 10 procedures/year

	c TUT: 12 procedures/year
Critical appraisal	Very little detail is provided regarding how the total costs were determine. There is no breakdown of costs or resource use and the costs included are not detailed. Chelation therapy is not included and is reported as $29,480/year (medication, supplies, home health fees). The costs are described as the 'average annual charge' and it is unclear what is meant by this; as this is a US study interprety this as hospital charges rather than resource costs.

Kalff (2010)	Australia
Design and Comparators	Before-and-after automated RBCX (Cobe) Annual costs of the automated RBCX programme was compared to the savings from reduced hospital admissions
Population	Adults with SCD requiring regular RBCX (n = 13); subgroup of patients with reliable hospital admission data receiving RBCX for frequent painful crises (n = 6)
Costs per year	Automated RBCX = AUD $25,400
Other outcomes	RBC used, procedure interval, HbS%, hospital admissions, ferritin, SCD-related events, adverse events, venous access
Results	Automated RBCX costs $25,400/year and saves $6,682 per patient per year (compared to pre-RBCX programme) Automated RBCX is not cost effective
Resources included	Device costs (purchasing and maintenance), consumables, pathology testing, RBC, nursing hours, hospital admissions
Assumptions	Outpatient RBCX: 5.5 x RBC units/procedure, procedure interval = 5 weeks, RBC = ~$300/unit. SCD painful crisis management: single RBCX treatment ($2443), 3 days hospital stay ($496/day). Mean reduction of 1.7 hospital admissions/patient/year
Critical appraisal	Costs were based on data from the finance departments and the Australian Red Cross Blood Service. The high cost of phenotype-matched RBC from the blood service was not passed onto the treating institution. From this we assume that this cost is included in the costs reported, but that this borne by the by the wider health service rather than the hospital. Pathology testing costs are included in the RBCX programme, but there are no costs for tests or analgesics for the crisis treatment. Although the clinical data in the main study indicates that painful crises form the majority of the hospital admissions there are also admissions for acute chest syndrome, which do not appear to be reduced in frequency by automated RBCX in this study. The cost of the RBCX programme includes the purchase and maintenance of the device, but it is not clear how many patients this cost is divided amongst or whether the purchase cost has been amortised over more than one year. This is a simplistic and hypothetical cost comparison incorporating little economic analysis.

Masera (2007)	Italy
Design and Comparators	Clinical data is reported for automated RBCX using Cobe Sepctra but the author also report a hypothetical comparison of calculated direct costs
Population	Hypothetical 30 *kg 10 year old paediatric patient with SCD
Costs per year	i automated RBCX (Cobe) = €3,928 c TUT = €7,074
Other outcomes	RBCX frequency, hospital admissions, complications, ferritin, RBC used, HbS%, HbF%
Results	Automated RBCX is not economically detrimental
Resources included	RBC units, IV pump (TUT), chelation therapy, consumables (needles, syringes), procedure cost
Assumptions	i automated RBCX: 3 RBC units/procedure, 4 procedures/year, cost of procedure = €523 c TUT: 14 RBC units/year (12 ml/kg/procedure), 12 procedures/year, daily desferoxamine 20 mg/kg, infusion pump (amortised over 5 years), No chelation therapy is required for automated RBCX. Hydroxyurea is not included.
Critical appraisal	Automated RBCX in this study has a relatively long interval between procedures (min 3 months). Costs are according to prices and reimbursement fees applied by local/national health authorities. The authors do not account for RBC wastage in TUT. They calculate 12 ml RBC per kg, i.e. 360 ml per procedure, where an RBC unit is 300 ml. Therefore each TUT procedure must use 2 RBC units, requiring 24 units per year. However the authors aggregate the units over the year and round down; 12 ml × 30 kg × 12 procedures = 4,320 ml, 4320/300 = 14.4 units. The RBC requirements for automated RBCX are 3 units per procedure or 12 units per year. The authors therefore substantially underestimate the use of RBC in TUT. The cost of the automated RBCX procedure is not broken down; we assume that consumables are included in this total. Costs for staff time, blood testing, complications and hospital admissions are not included in either arm. This is a simplistic and hypothetical cost summary incorporating little economic analysis.

Sarode (2011)	USA
Design and Comparators	Retrospective observational before-and-after intrapatient comparative study between deplation/RBCX and historical control (RBCX) n=6, plus calculated savings in RBC using device parameters n = 20
Population	Adults with SCA, stable with history of thrombotic stroke, n= 20
Costs	Saving per patient using automated depletion/RBCX rather than RBCX = $198,250 over 10 years

Other outcomes	HbS, procedure interval, FCR, RBC, procedure time, ferritin levels, chelation therapy, adverse reactions.
Results	
Resources included	RBC only
Assumptions	Depletion/RBCX uses 30.5 fewer units of RBC per year than RBCX (23.5 units due to fewer procedures combined with 1 less unit RBC per procedure). RBC unit = $650.
Critical appraisal	The calculated savings from reduced use of RBC are overestimated. The authors report the RBC required in ml/kg. There is a mean reduction of 1 RBC unit per procedure for depletion/RBCX (range 0.5-1.7 units) and 10/20 patients saved at least 1 whole unit of blood per procedure. For patients who saved <1 RBC unit this may represent wastage of the remainder of a unit. Therefore the average RBC saving per patient per year should be 23.5 + 3.5 = 27 units rather than 30.5 units.

8.2.2 Provide a complete quality assessment for each health economic study identified. A suggested format is shown in table C3.

See section 8.2.1

Table C3 Quality assessment of health economic studies – see Table C2

9 De novo cost analysis

Section 9 requires the sponsor to provide information on the de novo cost analysis.

The de novo cost analysis developed should be relevant to the scope.

All costs resulting from or associated with the use of the technology should be estimated using processes relevant to the NHS and personal social services.

Note that NICE cites the price of the product used in the model in the Medical Technology guidance.

9.1 Description of the de novo cost analysis

9.1.1 Provide the rationale for undertaking further cost analysis in relation to the scope.

No rigorous systematic analysis of the costs and benefits of conducting regular automated RBCX has been identified in the published literature. It is generally acknowledged as an expensive intervention in comparison to manual RBCX or TUT, but the analyses reported in section 8.2.1 have primarily included only the easily identified intervention costs. There is a general assumption that future savings from reduced or avoided chelation therapy would offset the additional technology and consumable costs. However, this assumption has not been rigorously tested, and full costs and benefits have not been included in any of the studies identified.

Patients

9.1.2 What patient group(s) is (are) included in the cost analysis?

We have included adults and paediatric patients with sickle cell disease requiring regular RBC transfusions. We have conducted separate analyses for subgroups in this population due to differences in indication, outcome rates and consumable use:

1. High-risk paediatric patients treated for primary stroke prevention
    a. with iron overload (previous transfusion treatment)
    b. without iron overload (no previous transfusion treatment)
2. Adult and paediatric patients being treated for prevention of SCD complications (e.g. secondary stroke or frequent crises – pain, ACS or priapism) refractory to hydroxyurea or in patients unable to take hydroxyurea
    a. with iron overload (previous transfusion treatment)
    b. without iron overload (no previous transfusion treatment)

Technology and comparator

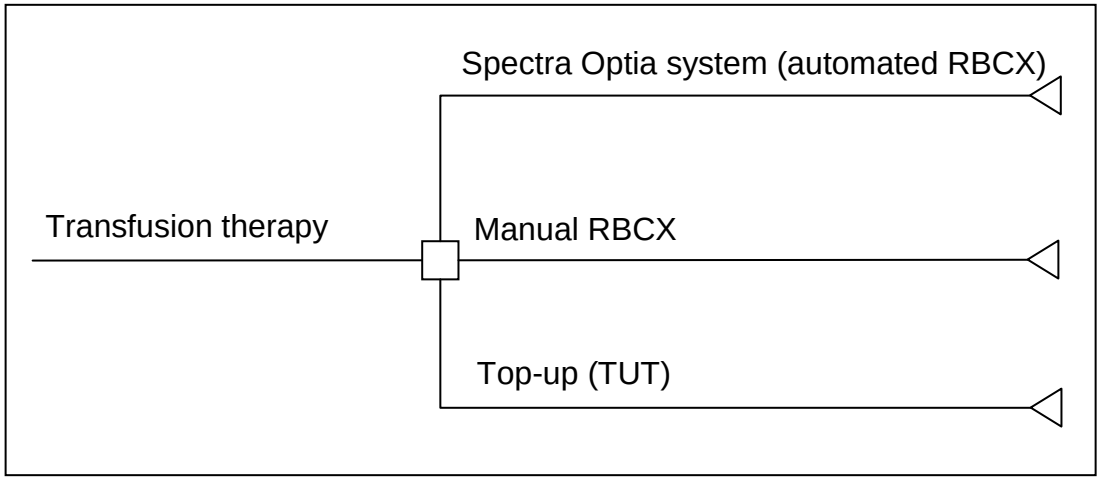
9.1.3 Provide a justification if the comparator used in the cost analysis is different from the scope.

We have additionally included top-up (simple) transfusions (TUT) for the reasons provided in section 1. Essentially, we believe that the use of automated RBCX rather than TUT at an earlier stage in the patient's transfusion pathway could provide superior clinical outcomes and an improved patient experience, and also avoid the need for iron chelation therapy in these SCD patients, thus reducing overall costs.`

Model structure

9.1.4 Provide a diagram of the model structure you have chosen.

Figure 3: Economic model structure



9.1.5 Justify the chosen structure in line with the clinical pathway of care identified in response to question 3.3.

The model is a three-arm decision tree, with a choice between automated RBCX, manual RBCX and TUT and a time horizon of 5 years. Most clinical outcomes (stroke, hospital admissions, etc.) have been included as an event rate per year or per 5 year period appropriate to the chosen transfusion therapy. This is the format in which this clinical data was reported. We have chosen not to represent these as health states as we have no data on which to base transition probabilities. Also we have no reason to assume that the occurrence of an events would alter subsequent transition probabilities. We have modelled changes in chelation therapy over 1year intervals to account for changes in the number of patients requiring chelation therapy over time and for ease of applying discounting.

The model structure is identical for each of the subgroup analyses, but some parameter values differ. We have not included a change of healthcare setting or infrastructure costs in the model as we assume that these do not change between the treatment modalities. Patients requiring regular transfusion therapy are likely to receive this treatment in a secondary care specialist haematology setting, primarily as outpatients.

The model provides per patient costs that do not include the capital and maintenance costs of the devices used: the Spectra Optia system for automated RBCX, blood warmer and IV pump. The cost of the use of a generic IV pump per manual RBCX procedure is considered negligible in these scenarios. Similarly a blood warmer may be used for each transfusion modality, is not specific to transfusions for SCD, is relatively low cost and may be replaced with a water bath. The technology costs of the Spectra Optia system are significant. However, this is a multi-purpose device and its use for regular automated RCBX in patients with SCD will comprise a variable proportion of its total workload depending on local circumstances. The effect of different service level provision is discussed in section 9.5.11.

Modelling adult and paediatric populations separately not only reflects the available clinical data but also ensures that the outcomes are relevant to NHS services that treat only adult or only paediatric patients.

9.1.6 Provide a list of all assumptions in the cost model and a justification for each assumption.

- 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 number and type of blood tests, before and after each transfusion procedure, are identical between modalities.
- Patients are compliant with the prescribed treatment regimes.
- Patients receive only one type of transfusion therapy over the time horizon of the model. Effects of emergency or ad hoc transfusion therapy that may be provided for treatment of crises or prior to surgery are not included.

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

- 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.

- 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.

- 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 infusion).

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

- Patients receiving automated RBCX do not preferentially require femoral or jugular central venous catheters (CVC) or implanted ports. Although some NHS services have included this as standard in their provision of automated RBCX, this has been based on an assumption of need rather than on an individual assessment of patients. There is a move away from this to the standard use of peripheral access in at least one NHS service. The routine use of CVC access for automated

RBCX is an unnecessary option for the majority of patients and is a decision for local service provision rather than a requirement of the technology.

Patients often have damaged peripheral veins as a result of multiple previous transfusions. Automated RBCX requires two venous access paths, whereas manual RBCX usually uses a single venous catheter. However, manual RBCX can be a comparatively aggressive procedure requiring significant and repeated negative and positive pressure (relative to venous blood pressure) applied at a single site. This may result in greater long term damage to the peripheral veins used. In contrast the Spectra Optia system uses continuous flow, from one arm to the other, with adjustable flow rates and incorporates pressure alarms to prevent additional damage to the vessels.

- Discounting is applied at 3.5% per year. Discount rates are taken from the HM Treasury Green Book (HM Treasury 2014).

- Patients need for iron chelation therapy changes over time depending on their starting iron levels and the mode of transfusion. The rates at which patients either start or cease chelation medication are not well-defined in the published literature and will vary between patients depending on therapy compliance and other unidentified factors. 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. (See the end of section 9.2.1 for a discussion of clinical advisers comments on these rates.)

  Patients starting regular transfusion therapy without iron overloading will start chelation therapy as follows (see section 9.2.1):

  - Automated RBCX – never need chelation

  - Manual RBCX – 10% after 24 months, 30% after 36 months, 50% after 48 months

- TUT – 90% after 12 months

Patients starting regular transfusion therapy with iron overloading will remain on chelation therapy if they are receiving manual RBCX or TUT. If they are receiving automated RBCX they will cease therapy depending on their starting serum ferritin levels as follows:

Table C2.1 Rate of cessation of chelation therapy in patients with iron overload and receiving automated RBCX

Iron overload	12 months	24 months	36 months	48 months
Mild	50%	100%	-	-
Moderate	5%	15%	30%	50%
Severe	0%	5%	15%	30%

9.1.7 Define what the model's health states are intended to capture.

Health states are not used in the model.

9.1.8 Describe any key features of the cost model not previously reported. A suggested format is presented below.

Table C4 Key features of model not previously reported

Factor	Chosen values	Justification	Reference
Time horizon of model	5 years	Although many studies were carried out over shorter time periods the longest mean or median follow-up period in the published evidence was 60.5 months for procedure outcomes (Sarode) and around 5 years for stroke (Hulbert; Adams).	Adams et al (2005) Hulbert et al (2006) Sarode et al (2011)
Discount of 3.5% for costs	3.5%		
Perspective (NHS/PSS)	The perspective is primarily secondary NHS care.	Although patients with SCD (particularly children) may have assistance from specialist social services, the outcomes identified in the decision problem are primarily related to secondary care interventions and outcomes. The published evidence and information from clinical advisers, NHS information leaflets and other SCD information sources did not suggest effects of automated RBCX on PSS resource use. A reduced rate of stroke will have significant effects on patients lifelong social care needs. The cost data for 2.5 years of stroke care uprated from Cherry et al (2012) does not include PSS costs but is still higher than the uprated cost for 5 years of stroke care from Youman (2003) which does include PSS costs.	Cherry et al (2012) Youman et al (2003)
Cycle length	1 year	Health states have not been used, but costs for each year of the model have been collated individually.	
NHS, National Health Service; PSS, Personal Social Services			

9.2 Clinical parameters and variables

9.2.1 Describe how the data from the clinical evidence were used in the cost analysis.

Values for the model variables were primarily derived from the clinical submission evidence. Mean values were used where appropriate. Where data

was sparse or missing we used data from studies that used alternative automated RBCX devices or where the device was not reported,

Procedure Time: This was calculated as the mean of the values identified in the clinical evidence. Quirolo et al (2015) indicated that procedure time was shorter for paediatric patients than for adults. Data for paediatric populations were taken from Dedeken, Quirolo, and Singer; for adults we used Kuo (2012b, 2015), Poullin (2014), Quirolo (2015), Shrestha (2015) and Sarode (2011).

Number of procedures per year: This was calculated as the mean of the values identified in the clinical evidence and supplemented with data from clinical advisers. Some data was calculated from procedure intervals where only this was reported. Although there appeared to be a difference between values for adults and paediatric patients, there was no comparative data to support this and no *a priori* reason why this should be the case. Primarily there appeared to be 2 groups of values for automated RBCX; around 10-11 procedures per year and around 7-8. However, the overall means appeared to be representative of each transfusion modality and retained the differences reported in studies where modalities were directly compared.

Number of RBC units used per procedure: This was calculated as the mean of the values identified in the clinical evidence and supplemented with data from clinical advisers. Only studies that reported units of RBC or where RBC units could be easily calculated from the reported values were used. Quirolo et al (2015) reported lower RBC usage in children than adults so that this variable was determined separately for these subgroups. Data for paediatric patients was taken from Adams (1996), Dedeken (2014), Quirolo (2015), Singer (1999) and two clinical advisers. Data for adults was taken from Asma (2015), Atassi (1998), Pocock (2004), Kalff (2010), Kuo (2015), Quirolo (2015), Shrestha (2015), Sarode (2011) and three clinical advisers. The mean was rounded up to the next whole number to account for wastage of units not completely transfused.

Number of staff per patient and staff grade: This information came primarily from clinical advisers and from the manufacturer. It is apparent that manual RBCX is far more labour-intensive than either automated RBCX or TUT. One clinical adviser indicated that they could not conduct manual RBCX as they did not have enough staff. We were advised that manual RBCX requires at least one clinical staff member to conduct the alternate venesections and transfusions and assistance from another to remove waste blood, deliver RBC units, change bags and conduct patient checks. Alternatively, two members of clinical staff may conduct the procedure simultaneously. Manual RBC is most often conducted by senior haematology nurses (Band 7) or junior doctors (F2 or Registrar) due to the technical difficulty of the procedure. Automated RBCX and TUT can be conducted by appropriately trained Band 5 nurses and do not require full-time attention once the procedure has commenced. At least one automated RBCX service conducts procedures simultaneously on two devices with a single nurse. Staff time per procedure was therefore based on 30 minutes, plus the procedure time multiplied by a factor that represented the number of staff required for that duration: 1 for automated RBCX, 1.5 for manual RBCX and 0.5 for TUT.

Rate of hospital admissions: We did not identify any studies that compared the rate of hospital admissions between different transfusion modalities. Three studies that used only automated RBCX reported mean rates of admission of 0.25 (ACS only, Kalff 2010), 1.02 (ACS and pain, Pocock 2004) and 0.69 (ACS and pain, Masera 2007) events per year. Webb et al (2014) reported a rate of 1.21 events per year using manual RBCX. In a study in which 12/17 patients received manual and the rest automated RBCX, Karafin et al (2014) reported 5.11 admissions for pain per year. In the STOP trial 63% of transfusions were TUT, and a further 25% were mixed TUT and RBCX. From this study Miller et al (2001) reported data that translates into a hospital admission rate (ACS and pain) of 0.21 events per year. Wallace et al (2014) reports data from 1984 to 2014 that is likely to include both TUT and RBCX procedures (and overlaps with Karafin 2014) and reports 1.1 events per year (ACS and pain).

It is complex to draw conclusions from this data, with generally small sample sizes, mixed populations, methods and context. The studies using only automated RBCX suggest a lower rate of hospital admissions. Given that 2/3 of these studies were in adults and that admissions for pain are known to increase with age, these low admission rates in patients treated with automated RBCX appear to be significant. The particularly high admission rate for pain only reported in Karafin (2014) cannot be easily explained. The rate is reported as 1.4 admissions per 100 days. It is possible that this rate is reported for the cohort of 17 patients or the subgroup of 13 patients in whom admission rates decreased from pre-transfusion regime values. This would produce rates of 0.30 or 0.39 admissions per year respectively, which appear more consistent with the other values. The particularly low admission rate reported in Miller (2001) is probably because this was the only study that reported hospital admissions in children being transfused for primary stroke prevention. This subgroup of SCD patients might be expected to have lower values of admissions for pain and ACS compared to the populations in the other studies who are being treated for serious complications and secondary stroke prevention.

On this basis it appears that automated RBCX has a tendency to reduce SCD-related hospital admissions. The period over which this effect occurs is difficult to quantify as follow-up periods in these studies are varied or not reported. Webb (2014) noted that the rate of hospital admissions was related to the interval between manual RBCX transfusions. Sturgeon (2009) reported that automated RBCX was conducted with intervals of 8 weeks or less had the lowest rates of hospital admission days (7.6, 0-34 per year) compared to larger intervals. This indicates that optimum transfusion regimes are required to obtain long term benefits.

For a population of patients being treated for secondary prevention we have chosen a value for automated RBCX of 0.65 admissions per year (the mean of the values from Kalff 2010, Pocock 2004 and Masera 2007). For manual RBCX and TUT we have chosen a value of 1.1 admissions per year (Webb 1998, Wallace 2014). For children being treated for primary stroke prevention

we have reduced these values proportionately to be consistent with Miller (2001) and have chosen 0.1 admissions per year for automated RBCX and 0.2 for manual RBCX and TUT. We have assumed that a difference in admission rates continues for as long as the transfusion regime continues.

Stroke rate: The STOP, STOP2 and SwiTCH trials, and an NIHR HTA report demonstrated the benefit of regular transfusions for children at high risk of primary stroke (Adams 1998; ; Adams 2005; Cherry 2012; Lee 2006; Ware 2012). These studies used a mixture of transfusion modalities and results were not reported separately. Stroke rates were either zero or very low (~0.01 per year) in transfused patients. We have no data regarding any disparate effect of different transfusion modalities on first stroke events. We therefore assume that there is no difference in the rate of first stroke between different transfusion methods and this outcome will not be included in the model for children treated for primary stroke prevention.

Hulbert (2006) was the only study identified in which secondary stroke rates were compared between different transfusion modalities; RBCX (automated and manual) versus TUT. Of 11 children with SCD in whom a first stroke was acutely treated with RBCX, followed by routine treatment with RBCX, none had a secondary stroke during 5 years of follow up. Of 18 other children acutely and routinely treated with TUT, 7 had a secondary stroke; translating to 0.07 strokes per year. The authors indicate that this result should be treated with caution due to the small number of cases and the lack of a biological basis to explain the difference. However, this study suggests that RBCX is superior to TUT in prevention of secondary strokes. Sarode et al (2011) reported no recurrent strokes over 60 months of follow up in patients receiving IHD-RBCX. Although the data for secondary stroke prevention is sparse, we have chosen recurrent stroke rates of 0.00, 0.01 and 0.07 for automated RBCX, manual RBCX and TUT respectively over a 5-year timeframe.

Iron chelation: Patients with SCD receiving regular TUT treatments will accumulate iron, primarily in their liver. Howard and Telfer (2015) recommend that chelation medication is commenced around 12 months after the start of chronic TUT therapy, depending on serum ferritin levels. In the STOP trial

serum ferritin levels increased to 1,804 ± 773 ng/ml after 12 months of regular transfusion therapy in which 63% of procedures were TUT (Adams 1998). At 24 months levels were 2,509 ± 974 ng/ml, but only 8/61 patients were on chelation therapy, and in the extended follow-up study ferritin levels at 48 months were 3,089 ± 771 ng/ml with 43/78 patients on chelation (Lee 2006). Chelation therapy is poorly tolerated by some patients and is generally contraindicated in pregnancy and breast-feeding (Joint Formulary Committee 2015), which may account for the low levels of medication therapy in this trial. Also, in a US setting patients may be discouraged from using chelation therapy due to its cost.

Chelation use in a UK setting may be higher. The National Haemoglobinopathies Registry Report indicates that 332 patients with SCD were receiving regular transfusion therapy and that around 250 were on chelation therapy (data from graph, National Haemoglobinopathies Registry 2014). Completeness and reliability of this data is questionable and the transfusion type is not reported separately, but this provides some evidence to support the conclusions that a high proportion of chronic TUT patients would be taking iron chelation therapy. Therefore for our model we assume that 90% of patients starting TUT will commence chelation therapy after 12 months and that this value will remain consistent over time.

For manual RBCX, Dedeken et al (2014) reported that 2/10 patients were taking iron chelation following 1.9 (0.5-4.4) years of treatment. Cabbibo et al (2005) report that in the 3 patients on manual RBCX who were not taking chelation therapy the serum ferritin increased an average of 16, 43 and 30 ng/ml per RBCX procedure. The article suggests that the first 2 patients should have been taking chelation therapy but were non-compliant. If we assume that SCD patients without iron overload have a normal starting serum ferritin level of 400 ng/ml, using the rates of increase from Cabibbo it would take 14, 20 and 37 procedures to reach ferritin levels of 1000 ng/ml. We assume that levels would have to remain high for at least 3 procedures before a patient would be started on chelation therapy. At 12 manual RBCX procedures per year (base case) this translates to approximately 1.5, 2 and

3.3 years into the regime. We therefore assume that the start of chelation therapy in manual RBCX corresponds approximately to the following regime:

Table C4.1 Initiation of chelation therapy in patients without initial iron overload receiving manual RBCX

After 12 months	After 24 months	After 36 months	After 48 months
0%	10%	30%	50%

Regular automated RBCX produces substantially lower net iron loading than TUT, despite the much higher volumes of RBCs used in each procedure (Kim 1994; Singer 1999). We did not identify any data on iron loading in manual RBCX. Fasano et al (2014) report the only study in which TUT, manual and automated RBCX were compared directly. There were statistically significant differences in the changes in serum ferritin (n=36) and liver iron concentration (LIC) (n = 23) over at least 6 months between the modalities, in children also taking iron chelation therapy. Serum ferritin and LIC increased in TUT and manual RBCX and reduced in automated RBCX. However, this study used partial manual exchange (a term not defined) and the period of measurement is short. Cabibbo et al (2005) also demonstrated an increase in serum ferritin in 7/7 patients on manual RBCX, whereas 5/13 on automated RBCX remained relatively stable and 7/13 decreased. Dedeken et al (2014) reported 10 children who transferred from manual to automated RBCX and experienced a reduction in serum ferritin. These results suggest that automated RBCX is superior to manual RBCX regarding the accumulation of iron.

Studies have shown that in patients not taking chelation, or with variable medication compliance, serum ferritin levels tend to remain stable in patients receiving automated RBCX over periods up to 60 months (Adams 1996; Cabibbo 2005; Kuo 2012b; Sarode 2011; Billard 2013; Kalff 2010; Singer 1999). In patients with iron overload and taking chelation therapy automated RBCX tends to reduce serum ferritin levels over time (Adams 1996; Fasano 2014; Kalff 2010; Singer 1999; Willis 2011).

Serum ferritin is not an ideal measure of iron overload but it is relatively easy to measure and is the most widely reported. Liver iron concentration can be assessed using biopsy, MRI (including the trademarked 'Ferriscan') and SQUID methods (superconducting quantum interference device). Todd et al (2015) reported that in patients with no iron overload and not on chelation therapy LIC did not increase over 36 months. However, in patients with significant initial iron overload, chelation therapy combined with automated RBCX reduced liver iron substantially. Vichinsky et al (2007) reported that reductions in LIC were substantially greater for automated RBCX than for TUT in patients taking deferasirox. The mean reduction in LIC for automated RBCX and deferasirox was 6.6 ± 5.6 mg/g over 12 months.

We conclude that, for patients not taking chelation medication, iron levels are likely to remain stable on automated RBCX for most patients. If patients begin automated RBCX before they have accumulated iron overload from chronic TUT then we assume that they will not require chelation therapy for the duration for the model. Although iron overload is related to mortality in SCD (Porter and Garbowski 2013) none of the studies we identified reported any adverse clinical outcomes from iron overload. It is likely that sequelae from iron overload would occur substantially beyond the time horizon of our model, therefore we have not included this in the model.

We assume patients starting the model with existing iron overload have been in receipt of regular TUT and that therefore 90% of these patients will be on iron chelation medication. This will remain constant in patients continuing to receive TUT, and for those starting manual RBCX we assume this to be 80% as iron loading is lower in manual RBCX.

Kim et al (1994) report that of 8 patients initially on chelation therapy 4 ceased taking medication after 20-46 months of automated RBCX. Sarode et al (2011) reported that 2/20 patients on chronic automated IHD-RBCX discontinued chelation medication (time point not reported). Adams et al (1996) reported that 1/3 patients who began automated RBCX with iron overload and chelation therapy ceased chelation therapy (time point not reported). Dedeken et al (2014) reported that 2/10 patients who were taking

chelation at moderate levels of serum ferritin were able to cease medication after 1 and 10 automated RBCX procedures (procedure interval of 34 days).

In patients with iron overload who are compliant with chelation medication we conclude that chronic automated RBCX treatments will gradually reduce iron levels and some patients will be able to discontinue chelation therapy within the tmie horizon of the model. Determining the proportion and rate of cessation is more difficult. The duration of automated RBCX therapy required before a patient can cease chelation therapy will depend partly on their initial iron levels. Patients with moderately increased levels of serum ferritin (e.g. around 1,500 ng/kg) may be able to cease medication within the first year of automated RBCX (Dedeken 2014). For increasing levels of ferritin it may take 2-8 years, but not all patients may achieve such substantial reductions in iron overload (Sarode 2011). In contrast Porter and Garbowski (2013) reported one patient who began automated RBCX with ferritin levels of around 4,000-6,000 ng/dL and achieved a reduction to around 1,000 ng/dL in approximately 18 months.

For the scenario in which patients enter the model with iron overload we have assumed different initial iron overload severities; the percentage of patients who can cease chelation therapy as detailed in Table C4.2 below. The percentages are cumulative. For example, after 36 months 100% of the patients with mild overload will have ceased chelation therapy, along with 30% of patients with moderate overload and 15% of those with severe overload.

Table C4.2 Cessation of chelation therapy in patients with initial iron overload receiving automated RBCX

Starting iron overload	After 12 months	After 24 months	After 36 months	After 48 months
Mild	50%	100%	-	-
Moderate	5%	15%	30%	50%
Severe	0%	5%	15%	30%

As 90% of patients starting the model are taking iron chelation this means that the proportion of patients taking chelation in each year is reduced as follows:

Table C4.3 Proportion of patients with initial iron overload and in receipt of automated RBCX who will take chelation therapy

Starting iron overload	1st year	2nd year	3rd year	4th year	5th year
Mild	0.9	0.45	0.0	0.0	0.0
Moderate	0.9	0.86	0.77	0.63	0.45
Severe	0.9	0.9	0.86	0.77	0.63

We received comments on the cessation rates for moderate and severe iron overload from two clinical advisers with extensive experience of using the Spectra Optia system for automated RBCX. They both indicated that they considered our estimate to be too conservative. One adviser stated that even severely overloaded patients should be able to cease chelation therapy in 18-24 months if they were compliant with their medication. The other suggested alternative (higher) cessation rates to those in Table C4.2 (see Table C10.2b). However, this information was received too late to be used as the base case for the model and incorporated into the full sensitivity analyses. Therefore we have included a scenario in the sensitivity analysis that adopts these suggested rates and conducted a threshold analysis for chelation costs over 5 years for automated RBCX (section 9.5.7, Table C14.6).

9.2.2 Are costs and clinical outcomes extrapolated beyond the study follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified?

The model duration has been chosen to match the available evidence for clinical outcomes. Stroke and hospital admission data is available for up to 5 years. Although admissions for pain crises are known to increase with age, we have assumed that hospital admission rates are constant over the period of the model. Costs for resource use and clinical outcomes are also consistent with the time horizon. For example, stroke has ongoing costs over the lifetime of the patient but we have only included the costs for the 5 years of the model. As we have determined a lower rate of stroke using automated RBCX this represents a substantial underestimate of the potential savings from the use of the Spectra Optia system.

9.2.3 Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what sources of evidence were used and what other evidence is there to support it?

No intermediate outcomes were used. Only outcomes for which published data was available were included.

9.2.4 Were adverse events such as those described in section 7.7 included in the cost analysis? If appropriate, provide a rationale for the calculation of the risk of each adverse event.

Adverse events have not been included in the model for the following reasons.

Mild-moderate reactions

Mild adverse events are relatively common with RBCX transfusion procedures. The most common are mild-moderate citrate reactions (paraesthesia and nausea), mild-moderate vasovagal episodes (light-headedness, hypotension, bradycardia) and other minor reactions (e.g. fever and rash) (Sarode 2012; Patel 2013). These are temporary, are associated with all apheresis procedures and are easily managed during the transfusion procedure. Citrate reactions are caused by hypocalcaemia and are managed with calcium tablets (e.g. Adcal or Calcichew) or infusion during the procedure. These treatment costs are negligible (2 Calcichew tablets = £0.44) and these events have not been included in the model.

Vasovagal episodes may require repositioning of the patient, pausing of the procedure and/or additional saline infusions. Again the costs of consumables are negligible, but the additional time required for the patient to recover may impact the model. An extra 30 minutes of nurse time would add £17 to the cost of automated RBCX. However, vasovagal reactions also occur in manual RBCX. We have no data to provide a robust comparison and no suggestion that rates are significantly different between the transfusion modalities, so these have not been included in the model. Some centres provide

prophylactic calcium and additional fluid volume as standard (University College London Hospitals NHS Foundation Trust 2015). Fever not related to haemolysis is treated with paracetemol and rash with an antihistamine. These are also negligible costs and are not included in the model.

Haemolytic transfusion reactions

Higher grade adverse events are acute and delayed haemolytic transfusion reactions (HTR). These are potentially life-threatening events and will result in a hospital stay of at least 5 days, some of which may be in the ICU. In the 2014 Serious Hazards of Transfusion (SHOT) report there were 2 acute and 9 delayed haemolytic transfusion reactions recorded in patients with SCD in the UK (1 delayed reaction followed a transfusion abroad) (Bolton-Mags 2015). Of these, 3 patients suffered major morbidity. This data is not reported separately for different transfusion modalities and this number will include patients receiving ad hoc or emergency transfusions. Numbers were similar in 2013 and generally less frequent prior to that. The total number of transfusions in this patient group is not reported and it is not known how complete reporting is for these outcomes although 99.5% of NHS organisations participate (Bolton-Mags 2013). However, it does indicate the overall low level of such adverse reactions in the UK.

Although these events are serious and potentially costly, they can occur following any of the transfusion modalities (Wahl 2012; Patel 2013). Given the rarity of these events we have no data to suggest that the incidence rates differ between modalities and these events have not been included in the model.

Other adverse events

Patel et al (2013) reported 6/166 procedures resulted in mild bleeding, and 4/166 in major bleeding requiring transfusion or readmission plus 1 line thrombosis. This transfusion service provided automated RBCX via femoral catheters inserted on the day unit or theatre, which may account for the disproportionate number of bleed events compared to other studies. Woods et al (2014) reported a large number of catheter complications using automated

RBCX (15/21 patients) compared to manual RBCX (1/17 patients) in a centre that used implantable double lumen large-bore ports for apheresis.

Asma et al (2015) reported maternal and foetal outcomes for women with SCD receiving automated RBCX during pregnancy. Maternal complication and maternal death were both significantly lower in the automated RBCX group than in the control group. However, there were 4 adverse events during 43 RBCX procedures: 1 anxiety, 1 allergic reaction and 2 citrate reactions. There were 8/43 (18.6%) procedures affected by access difficulties.

Alloimmunisation

There were initially concerns that the greater donor exposure in automated RBCX compared to manual RBCX and TUT would lead to increased levels of alloimmunisation. This does not seem to be the case. The rate of new antibody formation per unit of RBC is similar (Fasano 2015) or lower for automated RBCX than both TUT and manual RBCX (Venkateswaran 2011; Wahl 2012). These studies also suggest that the proportion of patients who develop alloantibodies is not higher in automated RBCX. In the 2014 Serious Hazards of Transfusion (SHOT) report two cases of alloimmunisation were reported, at least one of which was in a patient with beta thalassaemia (Bolton-Mags 2015).

There is a suggestion that there is a plateau effect in this response and also that some patients are more susceptible than others. For example Adams et al (1996) and Sarode et al (2011) reported additional alloimmunisation during automated RBCX only in patients who had existing antibodies from previous TUT regimes. Kalff et al (2010) reported that 8/10 patients who developed new alloantibodies during 6-119 months of automated RBCX had pre-existing alloimmunisations. However, alloimmunisation has no cost implications as the cost for a unit of blood is independent of the degree of cross-matching involved. All SCD patients on regular transfusion therapy should have full blood typing recorded with NHSBT and appropriate units should be ordered in advance. Increased levels of alloimmunisation may mean that it takes longer to identify appropriate blood units, with potential delays to patients' treatment.

Incidence rates

Rates of adverse reactions are difficult to determine across studies due to variable definitions and reporting conventions. In particular there is a lack of comparative data between transfusion modalities. Data from the STOP trial indicates a low rate of complications in TUT of around 0.4-1.0% of procedures but there is no detail about the type of event (Lee 2006). Atassi et al (1999) reports a very high rate of adverse events for manual RBCX; 45% (9/20) of procedures in 11 patients, of which 4 were vasovagal episodes.

Evidence suggests that some patients are particularly prone to transfusion reactions. In Patel et al (2013) 6/10 episodes of paraesthesia were experienced by 3/32 patients, and 1 patient experienced 2 vasovagal episodes, 3 paraesthesia and 1 rash during regular automated RBCX. This patient was continuing the programme. Sarode et al (2012) report that 2/20 patients accounted for 57% of all citrate reactions and 2 other patients accounted for 67% of all vasovagal reactions during regular IHD-RBCX procedures. Both patients continued in the programme, although another discontinued due to repeated vasovagal events.

Spackman et al (2014) conducted a cost-effectiveness analysis that included all transfusion reactions in patients with SCD having pre-operative transfusions. Although lifetime costs were high, extremely small probabilities of occurrence resulted in a per transfusion additional cost of £1.69 (2011 prices). We have no reason to expect that the consequences or likelihood of (non apheresis-related) adverse events are any different between the transfusion modalities, despite the increased donor exposure in automated RBCX. We have therefore not included the cost of adverse events in the economic model.

9.2.5 Provide details of the process used when the sponsor's clinical advisers assessed the applicability of available or estimated clinical model parameter and inputs used in the analysis.

The manufacturer provided a list of clinicians at hospitals around the UK who were involved in transfusions in patients with SCD. We attempted to contact

each person on this list. Some of the individuals were no longer at the location identified and were updated where information was provided. A short survey was sent to 32 individuals at 24 NHS organisations by email on 21st or 22nd June 2015 (see Figure 4 below). This was intended to get a better understanding of certain parameters and the UK clinical context. Written responses were obtained from 5 clinicians and 2 others responded by telephone. Four of these only provided regular transfusions as TUT, 1 provided TUT and manual RBCX, 1 provided automated RBCX and 1 provided TUT but had just started providing automated RBCX. Several of these also provided information about the conduct of manual RBCX as this was provided as one-off and emergency treatments.

Figure 4: Survey for clinical advisers

Resource	**Automated RBCX (Device name:)**	**Manual RBCX**	**Simple/top-up transfusion**
Number/grade of staff involved & staff time required			
Consumables: Blood Anticoagulant Saline Plasma Albumin Tubing/sets Other (please specify)			
Blood warmer			
IV pump			
Blood units used: Adults Children			
Interval between treatments (days)			
Percentage of patients using peripheral venous access			
Any additional procedures, e.g. CVC (provide details)			
Please state any differences in resource use for using depletion/exchange (isovolemic haemodilution)			
Percentage of patients			

requiring chelation therapy			
Percentage of procedures that have to be abandoned or converted to top-ups (reasons)			
Percentage of procedures that result in adverse events			
Number of patients (per year)			

Following further development of the economic model, clinicians who had responded were requested to comment on the assumptions underlying the model; specifically the rate at which patients either started or ceased chelation therapy. Response were received from 3 clinicians from 2 sites.

9.2.6 Summarise all the variables included in the cost analysis. Provide cross-references to other parts of the submission. A suggested format is provided in table C5 below.

See also section 9.2.1 for an explanation of the calculation of the proportion of patients either starting or ceasing chelation therapy and the rates of secondary stroke and hospital admissions.

Table C5 Summary of variables applied in the cost model

Variable	Auto RBCX	Manual RBCX	TUT	Source
Units of RBCs (rounded up) for adult patients	7	4	2	Mean of multiple studies; clinical advisers; hospital documents, see section 9.2.1
Units of RBCs (rounded up) for paediatric patients	5	4	2	
Procedures per year	8.5	12	13	
Procedure time for adults (mins)	110	245	300	
Procedure time for paediatric patients (mins)	86	245	180	
Number of staff per patient	1	1.5	0.5	Clinical advisers
Rate of secondary stroke over 5 years	0	0.01	0.07	Section 9.2.1
Rate of hospital admission per year (secondary prevention)	0.65	1.1	1.1	Section 9.2.1
Rate of hospital admission per year (primary prevention)	0.1	0.2	0.2	Section 9.2.1

9.3 Resource identification, measurement and valuation

NHS costs

9.3.1 Describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff.

The HRG (Healthcare Reference Group) code for red blood cell exchange is the same for manual and automated procedures:

- SA13A – Single Plasma Exchange, Leucopheresis or Red Cell Exchange with length of stay 2 days or less and 19 years and over
- SA13B – Single Plasma Exchange, Leucopheresis or Red Cell Exchange with length of stay 2 days or less and 18 years and under

Table C5.1 RBC exchange NHS Reference Costs and HRG codes

HRG code		NHS Reference Cost (2013-14)	PbR Tariff (2014-15)
SA13A (≥19 years)	Outpatient	£166	£158
	Day Case/ Elective	£496	£406
SA13B (≤18 years)	Outpatient	£188	£183
	Day Case/ Elective	£658	£615

Market Forces Factors may be applied to the tariff. One NHS business case for a Spectra Optia device indicated a top-up charge per procedure starting at £2,214 and decreasing to £1,136 by year 4 onwards. No HRG codes were identified for simple transfusion of red blood cells.

9.3.2 State the Office of Population, Censuses and Surveys Classification of Surgical Operations and Procedures (OPCS) codes for the operations, procedures and interventions relevant to the use of the technology for the clinical management of the condition.

Table C5.2 RBC exchange Relevant OPCS codes

X32.6	Red cell exchange
X32.8	Other specified exchange blood transfusion
X32.9	Unspecified exchange blood transfusion
X33.2	Intravenous blood transfusion of packed cells
X33.8	Other specified other blood transfusion
X33.9	Unspecified other blood transfusion
X34.8	Other specified other intravenous transfusion
X34.9	Unspecified other intravenous transfusion

Resource identification, measurement and valuation studies

9.3.3 Provide a systematic search of relevant resource data for the NHS in England. Include a search strategy and inclusion criteria, and consider published and unpublished studies.

We did not conduct a systematic search for resource data. Resource use data were taken primarily from the published literature included in the clinical evidence. This was supplemented for TUT using an NIHR Health Technology Assessment report on primary stroke prevention in children with SCD (Cherry

2012) and the studies it identified. Information was also obtained from clinical advisers. Costs were identified primarily from reference sources.

- Staff costs: PSSRU 2013-14 (Curtis 2014)
- Hospital admission costs: NHS Reference Costs (Department of Health 2014) and Hospital Episode Statistics online data (Health and Social Care Information Centre 2015)
- Medication costs: British National Formulary (Joint Formulary Committee 2015)
- Blood costs: NHS Blood and Tissue Services (NHSBT)
- Technology costs: manufacturer

Costs for a stroke in SCD: Cherry et al (2012) report costs for the treatment of stroke in SCD separated into the acute 3-month phase and ongoing 3-month cycles, according to stroke severity (mild/moderate/severe). Although we have determined a rate for secondary stroke over 5 years that differs by modality we do not have a model for when in the 5-year timeframe this will occur. As ongoing costs in stroke are significant, there will be a substantial difference in cost effect depending on the severity and whether the stroke occurs at the beginning or end of the 5-year horizon. Moderate severity strokes are the most likely to occur (Cherry 2012; Adams 1998), so for the base case we have chosen a moderate severity stroke occurring at the half-way point (2.5 years). This therefore incurs a base case cost of £8,161 + (9 × £1649) = £23,002. We have split this into the costs for the third, fourth and fifth years of the model, uprated to 2013/14 prices (using the NHS Pay and Prices Index, Curtis 2015) and applied 3.5% discounting to this to obtain a total of £21,807.

The range of cost of a stroke by severity and time of occurrence (from 12 months to 60 months) will be explored in the sensitivity analysis. Minimum cost is £3,420 (mild stroke occurs in the last 3 months of the 5 year period) and maximum cost is £114,031 (severe stroke occurs after 12 months; 15 × 3-month cycles of ongoing costs). Youman et al (2003) reported that the 5-year cost of stroke in the NHS was £15,000. Uprating this to 2013-14 costs (Pay and Prices Index) is £21,102. However, acute costs for stroke in SCD patients

are likely to include additional specialist treatments, such as red blood cell exchange transfusions.

Costs of hospital admissions: Cherry et al (2012) calculate per episode costs of £841 for a pain crisis and £1,815 for ACS. These are taken from Karnon et al (2000) but have been reduced to account for a reduction in hospital stay from 7 to 3 days. Uprating these values to 2013/14 prices (Pay and Prices index) results in £883 for a painful crisis and £1,905 for an ACS crisis. HES online primary diagnosis data for 2013-14 indicates that there were 9,372 emergency episodes with a diagnosis of sickle cell anaemia with crisis (D57.0, Health and Social Care Information Centre 2015). Mean length of stay was 3.4 days and median was 2.0 days, therefore approximately 50% of emergency SCD crisis admissions would be classed as a long stay (≥2 days). Long stay costs for Sickle Cell Anaemia with Crisis (HRG codes SA36A/B/C) vary between £1,910 and £3,832 and short stay between £423 and £962 depending on complication and co-morbidity (CC) score (Department of Health 2014). We have used the activity and total cost data from these reference sources to calculate the average cost of an SCD crisis admission as £1,355 (see below). This is similar to the midpoint in Cherry et al (2012). We will use the full range of these NHS Reference costs in the sensitivity analysis (£423 - £3,832).

Table C5.3 Cost of a sickle cell related inpatient stay

NHS Reference Costs 2013-14		**Non-Elective Inpatients – Long Stay**		
Code	Description	Activity	Unit Cost	Total Cost
SA36A	Sickle-Cell Anaemia with Crisis, with CC Score 6+	488	£3,832.31	£1,870,165.91
SA36B	Sickle-Cell Anaemia with Crisis, with CC Score 2-5	1,773	£2,663.20	£4,721,845.76
SA36C	Sickle-Cell Anaemia with Crisis, with CC Score 0-1	2,158	£1,909.86	£4,121,482.66
	Totals	4,419		£10,713,494.33
		Non-elective Inpatients – Short Stay		
		Activity	Unit Cost	Total Cost
SA36A	Sickle-Cell Anaemia with Crisis, with CC Score 6+	194	£962.06	£186,639.03
SA36B	Sickle-Cell Anaemia with Crisis, with CC Score 2-5	1,728	£511.20	£883,344.99
SA36C	Sickle-Cell Anaemia with Crisis, with CC Score 0-1	3,430	£422.66	£1,449,717.58
		5,352		£2,519,701.60
Total (long & short stay)		**9,771**		**£13,233,195.93**
Mean cost per episode				**£1,354.33**

Costs of chelation therapy: Costs of chelation are dependent on age (weight), severity of iron overload and choice of chelator. We have used the costs based on deferasirox (Exjade) rather than desferrioxamine. The latter is the older of the two medications indicated for iron overload in SCD and is given as a subcutaneous infusion, whereas Exjade is an oral medication that is taken once a day dispersed in liquid (Join Formulary Committee 2015). Clinical preference is for Exjade (Cherry 2012; Howard and Telfer 2015), which is available as 125, 250 and 500 mg tablets. Cherry et al (2012) determined values for annual chelation costs of between £4,688 and £7,688 that include medication and monthly creatinine and weekly neutrophil counts (£385 per 3 months). However, these values substantially underestimate medication costs for higher doses in children and are inappropriate in adults. We have therefore determined ranges of values for paediatric and adult populations.

The standard dose range is 10-30 mg/kg body weight for both adult and paediatric patients, but the dose can be increased to 40mg/kg. Doses should be increased and reduced gradually in 5-10mg/kg increments every 3 months (Joint Formulary Committee 2015; Howard and Telfer 2015). For a 3-year old

child at 15 kg the minimum dose would be 150 mg daily. They would likely be given 1 × 125mg tablet per day. Minimum annual medication cost is therefore £1,533 (13 packs of 28 tablets at £117.60 per pack).

Children and teenagers with SCD are known to be smaller and lighter than their peers in the general population (Bavle 2014; Thomas 2000). Example minimum (10 mg/kg) and maximum (30 mg/kg, except adults* at 40 mg/kg) annual medication costs are given below.

Table C5.4 Cost of minimum and maximum deferasirox doses (* maximum dose for adults calculated at 40 mg/kg)

Age (years)	Weight (kg)	Calculated dose (mg)	Dose taken (mg)	Packs per year	Annual cost
3	15	150	125	13 × 125 mg	£1,533
		450	500	13 × 500 mg	£6,119
7	20	200	250	13 × 250 mg	£3,058
		600	625 (500 + 125)	13 × 125 mg 13 × 500 mg	£7,652
15	40	400	375 (250 + 125)	13 × 125 mg 13 × 250 mg	£4,591
		1200	1250 (2 x 500 + 250)	13 × 250 mg 26 × 500 mg	£15,296
Adult*	70	700	750 (500 + 250)	13 × 250 mg 13 × 500 mg	£9,177
		2800	2750 (5 x 500 + 250)	13 × 250 mg 65 × 500 mg	£33,653*

In addition to the medication costs we will include the monitoring costs from Cherry et al (2012) of £1,540 per year. Therefore in a paediatric population we will use a range of annual chelation costs from £3,073 to £16,836 in the sensitivity analysis and the mean value of £9,954 for the base case. In an adult population we will use a range of £6,131 to £35,913 and a mean of £21,022 (50-70 kg, £12,237 + £1,540) for the base case. We have not accounted for titration of the dose either upwards when starting medication or downwards when ceasing. Given the uncertainty of time points when patients will start or stop chelation therapy, and actual frequencies of doses used this level of precision seems inappropriate. Medication costs will therefore be slightly overestimated during titration phases.

9.3.4 Provide details of the process used when clinical advisers assessed the applicability of the resources used in the model[1].

The process described in 9.2.5 was followed.

Technology and comparators' costs

9.3.5 Provide the list price for the technology.

Spectra Optia device:	£45,351.60
RBCX/RBC depletion software:	£6,700.85
Spectra Optia exchange set:	£1,007.04 per 6; £167.84 each
Astotube with injection port:	£218.50 per 50; £4.37 each
ACD-A anticoagulant (750 ml):	£57.36 per 12; £4.78 each
Service charge:	£4,572 per year

Note that there are bulk order discounts available on the sets. The Spectra Optia system is a multi-purpose apheresis device and the discounts apply on the total of all sets ordered. There are multiple levels of discount that start at 3% for 15-32 cases (each of 6 sets) up to 20% for 86+ cases. At maximum discount the cost for a single Spectra Optia RBC exchange set is £134.27. This has been included in the sensitivity analysis.

9.3.6 If the list price is not used in the de novo cost model, provide the alternative price and a justification.

The list prices are used in the model.

9.3.7 Summarise the annual costs associated with the technology and the comparator technology (if applicable) applied in the cost model. A suggested format is provided in tables C6 and C7. Table C7 should only be completed when the most relevant UK comparator for the cost analysis refers to another technology.

The procedure costs differ between adults and children due to different number of RBC units required and different procedure times. However, the

[1] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

procedure costs are independent of whether the procedure is for primary stroke prevention or secondary prevention.

Table C6 Costs per treatment associated with the technology in the cost model – Spectra Optia system

Items	Value adults	Value children	Source
Price of the technology per treatment	£167.84	£167.84	Manufacturer
Consumables RBC units Blood tests, access tubing, saline	 £840.00 £20.00	 £600.00 £20.00	 NHSBT Royal London Hospital
Maintenance cost	NA	NA	See section 9.5.11
Training cost	£0	£0	Manufacturer
Other costs (staff)	£79.33	£65.73	Curtis (2015)
Total cost per treatment	£1107.14	£853.57	

Table C7 Costs per treatment associated with the comparator technology in the cost model – not used

Health-state costs

9.3.8 If the cost model presents health states, the costs related to each health state should be presented in table C8. The health states should refer to the states in section 9.1.7. Provide a rationale for the choice of values used in the cost model.

Health states are not used in the model.

Table C8 List of health states and associated costs in the economic model – not used

Adverse-event costs

9.3.9 Complete table C9 with details of the costs associated with each adverse event referred to in 9.2.4 included in the cost model. Include all adverse events and complication costs, both during and after longer-term use of the technology.

Adverse event costs are not included in the model.

Table C9 List of adverse events and summary of costs included in the

cost model – not used

Miscellaneous costs

9.3.10 Describe any additional costs and cost savings that have not been covered anywhere else (for example, PSS costs, and patient and carer costs). If none, please state.

The per-procedure costs are higher for automated RBCX with the Spectra Optia system than for manual RBCX or TUT; savings in staff time are outweighed by the cost of consumables (device costs and RBC units). Cost savings from the use of the device arise from the reduction in the use of iron chelation medication and also from reductions in stroke and hospital admissions due to complications of SCD.

We have not included social services costs for patients who have a stroke.

Patients who do not have access to automated RBCX locally may travel long distances for treatment (e.g. Birmingham to London) for which they have to pay their own travel costs.

9.3.11 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

No.

9.4 Approach to sensitivity analysis

Section 9.4 requires the sponsor to carry out sensitivity analyses to explore uncertainty around the structural assumptions and parameters used in the analysis. All inputs used in the analysis will be estimated with a degree of imprecision. For technologies whose final price/acquisition cost has not been confirmed, sensitivity analysis should be conducted over a plausible range of prices.

Analysis of a representative range of plausible scenarios should be presented and each alternative analysis should present separate results.

9.4.1 Has the uncertainty around structural assumptions been investigated? State the types of sensitivity analysis that have been carried out in the cost analysis.

The following structural assumptions have been tested using multiple 1-way sensitivity analyses:

- The timing and severity of a secondary stroke
- The cost of hospital admission for a sickle cell crisis (varies by crisis type)
- The dose of chelation medication
- The grade of staff conducting each procedure
- The ratio of staff to patients during the procedure
- The number of RBC units per procedure, number of procedures per year and procedure duration
- The cost of a Spectra Optia exchange set
- The cost of blood tests and miscellaneous consumables (e.g. venous access, saline).

The level of influence of each variable on the overall costs and rankings of the three treatment options was investigated using tornado diagrams and the effect of the most influential variables and those that produced a change of treatment ranking were investigated with threshold analyses.

Scenarios were also used to investigate sets of changes to the base case values:

- Use of depletion/RBCX (IHD-RBCX) protocol – reduce the number of RBC units used in automated RBCX by 1 (Quirolo 2015; Sarode 2011).
- 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

9.4.2 Was a deterministic and/or probabilistic sensitivity analysis undertaken? If not, why not? How were variables varied and what was the rationale for this? If relevant, the distributions and their sources should be clearly stated.

A deterministic approach to the sensitivity analysis was conducted. The range of values for the model variables and costs were described in earlier sections. These values were taken from the published clinical evidence, clinical advisers, manufacturer and reference sources.

9.4.3 Complete table C10.1, C10.2 and/or C10.3 as appropriate to summarise the variables used in the sensitivity analysis.

Table C10.1a Variables used in one-way scenario-based deterministic sensitivity analysis – variables that differ between transfusion modalities

Variable	Auto RBCX			Manual RBCX			TUT			Source
	Base	Min	Max	Base	Min	Max	Base	Min	Max	
Units RBC (rounded up) for adult patients	7	4	14	4	2	8	2	1	3	Mean of multiple studies; clinical advisers
Units RBC (rounded up) for paediatric patients	5	4	14	4	2	8	2	1	3	Mean of multiple studies; clinical advisers
Procedures per year	8.5	6	13	12	4	17	13	9	17	Mean of multiple studies
Procedure time for adult patients (mins)	110	60	180	245	120	360	300	120	360	Mean of multiple studies
Procedure time for paediatric patients (mins)	86	60	155	245	120	360	180	60	360	Mean of multiple studies
Number of staff per patient	1	0.5	1	1.5	1	2	0.5	0.2	1	Clinical advisers
Rate of secondary stroke (5 years)	0	0	0.01	0.01	0.005	0.015	0.07	0.035	0.105	Section 9.2.1; parity or ±50% for sensitivity
Rate of hospital admission/year (secondary prevention)	0.65	0.2	1.1	1.1	0.6	1.6	1.1	0.6	1.6	Section 9.2.1; ±50% for sensitivity
Rate of hospital admission/year (primary stroke prevention)	0.1	0.05	0.2	0.2	0.1	0.3	0.2	0.1	0.3	Section 9.2.1; parity or ±50% for sensitivity

Table C10.1b Variables used in one-way scenario-based deterministic sensitivity analysis – variables constant across transfusion modalities

Variable	Base	Min	Max
Cost of blood tests per procedure	£20.00	£10.00	£30.00
Cost of nurse per hour (band 5, band 6)	£34.00	£34.00	£42.00
Cost of senior haematology clinician per hour (F2, Registrar, Band 7 nurse)	£40.00	£29.00	£51.00
Cost of a hospital admission	£1,355.00	£423.00	£3,832.00
Chelation costs per year (paediatric)	£6,895.00	£3,073.00	£16,836.00
Chelation costs per year (adult)	£13,777.00	£6,131.00	£35,193.00
Cost of the Optia exchange set for each procedure	£167.84	£134.27	£167.84
Cost of stroke episode	£21,807.00	£3,420.00	£114,031.00

Table C10.2a Variables used in multi-way scenario-based sensitivity analysis – change of chelation dose

Variable	Chelation cost - adult	Chelation cost – paediatric
Base case	£21,022	£9,954
Mild overload, low chelation	£6,131	£3,073
Severe overload, high chelation	£35,931	£16,836

Increased rate of chelation cessation: We increased the rate at which patients with moderate or severe overload cease chelation therapy after starting regular automated RBCX. This was in response to two clinical advisers indicating that our initial rates were too conservative. We used values suggested by a clinical adviser with several years of experience with the Spectra Optia system.

Table C10.2b Variables used in multi-way scenario-based sensitivity analysis – increased rate of chelation cessation, cessation rates

Starting iron overload	After 12 months	After 24 months	After 36 months	After 48 months
Moderate	10%	40%	80%	100%
Severe	0%	30%	60%	80%

As 90% of patients starting the model are taking iron chelation this means that the proportion of patients taking chelation in each year is reduced as follows:

Table C10.2c Variables used in multi-way scenario-based sensitivity analysis - increased rate of chelation cessation, proportion of patients taking medication

Starting iron overload	1st year	2nd year	3rd year	4th year	5th year
Moderate	0.9	0.81	0.54	0.18	0.0
Severe	0.9	0.9	0.63	0.36	0.18

Table C10.3 Variable values used in probabilistic sensitivity analysis – not used

9.4.4 If any parameters or variables listed in section 9.2.6 were omitted from the sensitivity analysis, provide the rationale.

The following variables were not included in the sensitivity analysis:

- The cost of a unit of packed red blood cells. This is a standard cost and does not vary according to purchaser or volume.
- Capital and maintenance costs of the Spectra Optia system. This has not been included in the model and the effect of different procurement and service configurations will be considered in 9.5.11.

9.5 Results of de novo cost analysis

Section 9.5 requires the sponsor to report the de novo cost analysis results. These should include the following:

- costs
- disaggregated results such as costs associated with treatment, costs associated with adverse events, and costs associated with follow-up/subsequent treatment
- a tabulation of the mean cost results
- results of the sensitivity analysis.

Base-case analysis

9.5.1 Report the total costs associated with use of the technology and the comparator(s) in the base-case analysis. A suggested format is presented in table C11.

Table C11 Base-case results – 5 year total costs per patient

Population	Option	No overload	Mild overload	Moderate overload	Severe overload
Adults	Optia	£48,093	£76,153	£119,779	£128,310
	Manual	£66,891	£128,670	£128,670	£128,670
	TUT	£99,981	£118,895	£118,895	£118,895
Paediatric secondary prevention	Optia	£38,020	£51,307	£71,964	£76,003
	Manual	£58,041	£87,293	£87,293	£87,293
	TUT	£61,325	£70,281	£70,281	£70,281
Paediatric primary prevention	Optia	£34,538	£47,824	£68,481	£72,520
	Manual	£52,124	£81,377	£81,377	£81,377
	TUT	£54,097	£63,056	£63,056	£63,056

9.5.2 Report the total difference in costs between the technology and comparator(s).

In the population where patients start regular transfusion therapy without iron overload automated RBCX with the Spectra Optia system is always cost saving in comparison to both manual RBCX and TUT. TUT is the most expensive option in this case.

In the population where patients already have iron overload, automated RBCX remains cost saving with respect to manual RBCX. However, TUT is ranked second for cost with mild overload and becomes the cheapest option as iron overload increase. Note that we have not altered the chelation dose between the populations with different iron loading. In reality chelation medication costs would be lower in the mild case and higher in the severe case. We have examined the effect of different medication costs in the sensitivity analysis.

Table C11.1 Base-case results – difference in 5 year costs per patient between treatment options

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

9.5.3 Provide details of the costs for the technology and its comparator by category of cost. A suggested format is presented in table C12.

Table C12a summarises the category costs for patients without iron overload. All category costs remain the same for the iron overload sub-groups, with the exception of chelation therapy. Therefore chelation costs for these subgroups are presented in Table C12b.

Table C12a Summary of costs by category of cost per patient – 5 year costs for patients without iron overload

Item		Consumables	RBC units	Staff	Hospital admissions	Chelation medication	Stroke	5 year total
Adults	Optia	£7,461.10	£33,365.22	£3,151.14	£4,115.74	£0.00	£0.00	£48,093.21
	Manual	£1,121.52	£26,916.48	£14,860.14	£6,965.11	£16,809.61	£218.07	£66,890.93
	TUT	£1,214.98	£14,579.76	£6,196.40	£6,965.11	£69,498.48	£1,526.49	£99,981.21
Paediatric secondary	Optia	£7,461.10	£23,832.30	£2,610.95	£4,115.74	£0.00	£0.00	£38,020.09
	Manual	£1,121.52	£26,916.48	£14,860.14	£6,965.11	£7,959.42	£218.07	£58,040.74
	TUT	£1,214.98	£14,579.76	£4,130.93	£6,965.11	£32,907.80	£1,526.49	£61,325.07
Paediatric primary	Optia	£7,461.10	£23,832.30	£2,610.95	£633.19	£0.00	£0.00	£34,537.54
	Manual	£1,121.52	£26,916.48	£14,860.14	£1,266.38	£7,959.42	£0.00	£52,123.94
	TUT	£1,214.98	£14,579.76	£4,130.93	£1,266.38	£32,907.80	£0.00	£54,099.86

Table C12b Summary of costs by category of cost per patient – 5 year costs for patients with iron overload

		Mild iron overload		Moderate iron overload		Severe iron overload	
		Chelation medication	5 year total	Chelation medication	5 year total	Chelation medication	5 year total
Adults	Optia	£28,059.96	£76,153.18	£71,685.02	£119,779.38	£80,216.48	£128,309.69
	Manual	£78,588.64	£128,669.96	£78,588.64	£128,669.96	£78,588.64	£128,669.96
	TUT	£88,412.23	£118,894.96	£88,412.23	£118,894.96	£88,412.23	£118,894.96
Paediatric secondary	Optia	£13,286.50	£51,306.60	£33,943.14	£71,963.78	£37,982.82	£76,002.91
	Manual	£37,212.03	£87,293.35	£37,212.03	£87,293.35	£37,212.03	£87,293.35
	TUT	£41,863.54	£70,280.81	£41,863.54	£70,280.81	£41,863.54	£70,280.81
Paediatric primary	Optia	£13,286.50	£47,824.05	£33,943.14	£68,481.23	£37,982.82	£72,520.37
	Manual	£37,212.03	£81,376.56	£37,212.03	£81,376.56	£37,212.03	£81,376.56
	TUT	£41,863.54	£63,055.59	£41,863.54	£63,055.59	£41,863.54	£63,055.59

9.5.4 If appropriate, provide details of the costs for the technology and its comparator by health state. A suggested format is presented in table C13.

Health states were not used in this model.

Table C13 Summary of costs by health state per patient – not used

9.5.5 If appropriate, provide details of the costs for the technology and its comparator by adverse event. A suggested format is provided in table C14.

Adverse events were not included in this model.

Table C14 Summary of costs by adverse events per patient – not used

Sensitivity analysis results

9.5.6 Present results of deterministic one-way sensitivity analysis of the variables described in table C10.1.

Tornado analysis was used to indicate the variables that were most influential in the cost of automated RBCX and the ranking of the treatment options by cost.

In patients without pre-existing iron overload, automated RBCX using Spectra Optia systems was consistently the lowest cost treatment option. The cost outcome for automated RBCX and treatment ranking were most strongly influenced by:

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

As the number of RBC units or number of automated RBCX procedures increases, automated RBCX obviously becomes more expensive than manual RBCX. As the number of manual RBCX procedures reduces it becomes cheaper than automated RBCX. Two-way analysis shows that there is not a constant difference or ratio between the two procedure frequencies; as the number of procedures per year decreases in both modalities, automated RBCX becomes more cost-saving with respect to manual RBCX.

As the difference in costs is relatively large in comparison to the total costs in this subgroup, changes in ranking tend to occur towards the ends of the sensitivity ranges. Automated RBCX is no longer the lowest cost option under the following circumstances:

Table C14.1 Results of 1-way sensitivity analysis – no iron overload

No iron overload	Variable	Threshold	Value of Automated RBCX	Ranking
Adults	Number of RBC units used per automated RBCX procedure	≥11	£66,890	1 manual 2 automated 3 TUT
	Number of automated	>12.1	£66,890	1 manual

	RBCX procedures per year			2 automated 3 TUT
	Number of manual RBCX procedures per year	<6.7	£48,093	1 manual 2 automated 3 TUT
Children, secondary prevention	Number of RBCX units used per automated RBCX procedure	≥10	£61,852	1 manual 2 TUT 3 automated
	Number of manual RBCX procedures per year	<6.4	£38,020	1 manual 2 automated 3 TUT
Children, primary prevention	Number of automated RBCX procedures per year	>12.9	£52,124	1 manual 2 automated 3 TUT
	Number of RBC units used per automated RBCX procedure	≥9	£53,603	1 manual 2 TUT 3 automated
	Number of manual RBCX procedures per year	<7.1	£34,538	1 manual 2 automated 3 TUT
	Cost of annual chelation therapy	<£4,037	£34,538	1 TUT 2 automated 3 manual

In patients with mild iron overload automated RBCX with the Spectra Optia system is consistently the lowest cost treatment option. Chelation costs become significant, but the overall cost difference from TUT (the next lowest cost option) is large so that a change in the ranking only occurs at the lowest end of this range. Automated RBCX with the Spectra Optia system is no longer the lowest cost option under the following circumstances:

Table C14.2 Results of 1-way sensitivity analysis – mild iron overload

Mild iron overload	Variable	Threshold	Value of automated RBCX	Ranking
Adults	Cost of chelation therapy	<£6,134.11	£56,281	1 TUT 2 automated 3 manual
Children, secondary prevention	Cost of chelation therapy	<£3,344.86	£42,485	1 TUT 2 automated 3 manual
	Number of RBC units used per automated RBCX procedure	≥9	£70,372	1 TUT 2 automated 3 manual
Children, primary prevention	Number of automated RBCX procedures per year	>12.3	£63,056	1 TUT 2 automated 3 manual
	Cost of chelation therapy	<£4,648.52	£40,742	1 TUT 2 automated 3 manual

	Number of RBC units used per automated RBCX procedure	≥9	£66,890	1 TUT 2 automated 3 manual

In patients with moderate iron overload TUT is marginally lower cost than automated RBCX. The primary cost driver in these patients is the cost of chelation medication, but the costs for automated RBCX and TUT are very close, and so several variables produce a change of treatment ranking. The number of RBC units per procedure and the number of procedures per year are prominent amongst these variables. TUT is no longer the lowest cost ranked option under the following circumstances:

Table C14.3 Results of 1-way sensitivity analysis – moderate iron overload

Moderate iron overload	Variable	Threshold	Value of automated RBCX	Ranking
Adults	Cost of chelation therapy	>£22,134	£123,570	1 automated 2 TUT 3 manual
	Number of manual RBCX procedures per year	<9.3	£71,964	1 manual 2 TUT 3 automated
	Number of RBC units used per automated RBCX procedure	≤6	£115,013	1 automated 2 TUT 3 manual
	Cost of a hospital admission	>£1,776	£121,057	1 automated 2 TUT 3 manual
	Number of automated RBCX procedures per year	<8.3	£118,895	1 automated 2 TUT 3 manual
	Number of RBC units used per TUT procedure	≥3	£119,779	1 automated 2 TUT 3 manual
	Number of TUT procedures per year	>13.5	£119,779	1 automated 2 TUT 3 manual
	Rate of hospital admissions per year – TUT	>1.24	£119,779	1 automated 2 TUT 3 manual
	Procedure time for TUT (minutes)	>351	£119,779	1 automated 2 TUT 3 manual
	Number of staff per patient – TUT	>0.6	£119,779	1 automated 2 TUT 3 manual

	Number of RBC units used per manual RBCX procedure	≤2	£119,779	1 manual 2 TUT 3 automated
	Cost of a stroke episode	>£34,442	£119,779	1 automated 2 TUT 3 manual
	Rate of hospital admissions per year – automated RBCX	<0.51	£118,895	1 automated 2 TUT 3 manual
	Cost of an Optia set	<£145.57	£118,895	1 automated 2 TUT 3 manual
	Number of staff per patient – automated RBCX	<0.6	£118,895	1 automated 2 TUT 3 manual
	Procedure time for automated RBCX (minutes)	<71	£118,895	1 automated 2 TUT 3 manual
Children, secondary prevention	Cost of chelation therapy	>£12,069	£79,177	1 automated 2 TUT 3 manual
	Cost of a hospital admission	>£2,155	£74,395	1 automated 2 TUT 3 manual
	Number of manual RBCX procedures per year	<7.2	£71,964	1 manual 2 TUT 3 automated
	Number of RBC units used per TUT procedure	≥3	£71,964	1 automated 2 TUT 3 manual
	Number of automated RBCX procedures per year	<8.1	£70,281	1 automated 2 TUT 3 manual
	Number of TUT procedures per year	14.1	£71,964	1 automated 2 TUT 3 manual
	Rate of hospital admissions – TUT	1.37	£71,964	1 automated 2 TUT 3 manual
	Procedure time for TUT	277.8	£71,964	1 automated 2 TUT 3 manual
	Number of staff per patient – TUT	0.8	£71,964	1 automated 2 TUT 3 manual
	Number of RBC units used per automated RBCX procedure	≤4	£71,964	1 automated 2 TUT 3 manual
	Cost of a stroke episode	£45,850	£71,964	1 automated 2 TUT 3 manual
	Rate of hospital admissions – automated RBCX	<0.38	£70,281	1 automated 2 TUT 3 manual

Children, primary prevention	Cost of chelation therapy	>£16,773	£68,481	1 automated 2 TUT 3 manual
	Number of RBC units used per TUT procedure	≥3	£68,481	1 automated 2 TUT 3 manual
	Number of TUT procedures per year	>16.5	£68,481	1 automated 2 TUT 3 manual
	Number of manual RBCX procedures per year	<6.9	£68,481	1 manual 2 TUT 3 automated

In patients with severe iron overload TUT is the lowest cost treatment option. The most influential cost driver for the overall costs is the cost of chelation therapy. However, this variable does not alter the ranking of the treatment options. The variables that alter the cost rankings differ between each subgroup but primarily comprise the number of procedures per year and the number of RBC units used. TUT is no longer the lowest cost treatment option under the following circumstances:

Table C14.4 Results of 1-way sensitivity analysis – severe iron overload

Severe iron overload	Variable	Threshold	Value of automated RBCX	Ranking
Adults	Number of manual RBCX procedures per year	<9.3	£128,310	1 manual 2 TUT 3 automated
	Number of RBC units used per automated RBCX procedure	≤5	£118,777	1 automated 2 TUT 3 manual
	Number of RBC units used per manual RBCX procedure	≤2	£128,310	1 manual 2 TUT 3 automated
	Number of automated RBCX procedures per year	<6.7	£118,895	1 automated 2 TUT 3 manual
Children – secondary prevention	Number of RBC units used per TUT procedure	≥3	£128,310	1 automated 2 TUT 3 manual
	Number of TUT procedures per year	>16.7	£128,310	1 automated 2 TUT 3 manual
	Number of manual RBCX procedures per year	<7.2	£128,310	1 TUT 2 manual 3 automated
	Cost of a stroke episode	>£103,552	£128,310	1 automated 2 TUT

				3 manual
Children – primary prevention	Number of manual RBCX procedures per year	<6.9	£72,520	1 manual 2 TUT 3 automated
	Number of automated RBCX procedures per year	<6.1	£63,056	1 automated 2 TUT 3 manual

One extra RBC unit for each automated RBCX procedure would cost an additional £1,050 per year over 5 years. The tornado analysis also indicated that the model results for automated RBCX were relatively robust to changes in stroke rate and costs, procedure time, staff grades and ratio of staff to patients. As patients receiving automated RBCX do not have any chelation costs, increasing medication costs only increases the difference between the modalities.

9.5.7 Present results of deterministic multi-way scenario sensitivity analysis described in table C10.2.

Depletion/RBCX: Reducing the number of RBC units per automated procedure by 1 unit reduces the 5 year blood costs by 8.5 (procedures per year) × £120 × 4.6727 (5 years with discounting) = £4,766.15 per patient.

Mild overload, low chelation dose and severe overload, high chelation dose: In the base case for mild iron overload the Spectra Optia system was the lowest cost treatment option in all subgroups. By reducing the chelation costs to the minimum clinical dose automated RBCX remains substantially cost-saving with respect to manual RBCX, but is cost neutral or moderately cost-incurring with respect to TUT.

In the base case for patients with severe iron overload, automated RBCX with the Spectra Optia system was cost-saving with respect to manual RBCX and moderately cost incurring with respect to TUT. With chelation doses at the maximum automated RBCX is approximately cost-neutral over 5 years in adults, whereas in children it remains cost-saving in comparison to manual RBCX.

Table C14.5 Results of scenario sensitivity analysis – chelation dose matched to iron overload

		Mild overload, low chelation		Severe overload, high chelation	
		Base case	**New value**	**Base case**	**New value**
Adults	Optia	£76,153	£56,277	£128,310	£185,131
	Manual RBCX	£128,670	£73,001	£128,670	£184,338
	TUT	£118,895	£56,268	£118,895	£181,522
Children, secondary prevention	Optia	£51,307	£42,122	£51,307	£102,263
	Manual RBCX	£87,293	£61,569	£87,293	£113,021
	TUT	£70,281	£41,341	£70,281	£99,224
Children, primary prevention	Optia	£47,824	£38,639	£47,824	£98,781
	Manual RBCX	£81,377	£55,653	£81,377	£107,104
	TUT	£63,056	£34,116	£63,056	£91,999

Increased rate of chelation cessation:

We increased the rate at which patients with moderate and severe iron overload were assumed to cease chelation therapy once they commenced regular automated RBCX. This has the obvious effect of reducing overall costs for the automated RBCX treatment option. Automated RBCX with the Spectra Optia system is then substantially or moderately cost-saving for all patient subgroups, except children with severe iron overload being treated for primary stroke prevention; in which circumstance it is approximately cost-neutral.

Table C14.6 Results of scenario sensitivity analysis – total 5 year costs, increased rate of chelation cessation in automated RBCX

		Moderate overload		Severe overload	
		Base case	**Scenario**	**Base case**	**Scenario**
Adults	Optia	£119,779	£97,475	£128,310	£107,779
	Manual	£128,670		£128,670	
	TUT	£118,895		£118,895	
Children, secondary prevention	Optia	£71,964	£61,403	£76,003	£66,282
	Manual	£87,293		£87,293	
	TUT	£70,281		£70,281	
Children, primary	Optia	£68,481	£57,920	£72,520	£62,799
	Manual	£81,377		£81,377	

prevention	TUT	£63,056		£63,056	

In this scenario treatment with automated RBCX is always cost saving in comparison to manual RBCX in the base case. We used a threshold analysis to determine the maximum chelation costs for automated RBCX that would result in this also being cost saving in comparison to TUT. The costs for TUT are the same for patients with moderate and severe overload, therefore the threshold is also the same.

Table C14.7 Results of scenario sensitivity analysis – 5 year chelation costs, increased rate of chelation cessation in automated RBCX

	Moderate overload			Severe overload		
	Base case	**Scenario**	**Threshold**	**Base case**	**Scenario**	**Threshold**
Adults	£71,685	£49,382	£70,801	£80,216	£59,686	£70,801
Children – secondary prevention	£33,943	£23,382	£32,260	£37,983	£28,262	£32,260
Children – primary prevention	£33,943	£23,382	£28,518	£37,983	£28,262	£28,518

This shows that automated RBCX is the lowest cost treatment option in adults where mean chelation costs for this modality over 5 years are £70,800 or less. At the base case annual cost of £21,022 this is equivalent to requiring chelation medication on average for the first 3.4 years of regular automated RBCX treatment. In children, the threshold is £28,518 to £32,260 depending on indication. At the base case annual cost of £9,954 this is equivalent to requiring chelation medication for the first 2.9 to 3.2 years of automated RBCX treatment.

Assuming that patients are compliant with their chelation medication, clinical advisers indicate that, in most cases, they should be able to cease at an earlier timepoint than this.

9.5.8 Present results of the probabilistic sensitivity analysis described in table C10.3.

Not conducted.

9.5.9 What were the main findings of each of the sensitivity analyses?

The cost of chelation therapy is the primary driver that determines the cost savings for automated RBCX with the Spectra Optia system. In the absence of chelation costs, TUT is consistently the lowest cost option, followed by automated RBCX.

Overall cost ranking are significantly dependent on the number of RBC units used per procedure and the number of procedures per year. Total costs are primarily driven by costs for chelation therapy and RBC units. Therefore any systematic change in RBC usage for each procedure has a significant effect on the relative costs between modalities.

Manual RBCX becomes lower cost than automated RBCX in only 8 of 48 1-way sensitivity analyses. Of these, 6 relate to the number of manual RBCX procedures per year. In the base case this was 12 procedures per year. In the 1-way sensitivity analyses manual RBCX becomes cost saving in comparison to automated RBCX when there are fewer than 6.9, 7.2 or 9.3 manual procedures per year for children treated for primary prevention, children treated for secondary prevention, and adults respectively. The frequencies for children translate to procedure intervals of 7.2 and 7.5 weeks (51-53 days) which are uncommon in the published literature and outside the ranges provided by the clinical advisers. The value for adults is reasonably likely. The other 2 analyses in which manual RBCX is lower cost than automated RBCX are when only 1 or 2 RBCX units are used for manual RBCX in adults. This is an extremely unlikely situation.

By implementing depletion/RBCX protocols as standard when using the Spectra Optia system in those patients in whom it is suitable costs for RBC units could be reduced by an average of £4,766 per patient over 5 years.

We changed the chelation costs for mild and severe iron overload to better reflect typical doses in those patient groups. Automated RBCX remained cost-saving or cost-neutral with respect to manual RBCX for all subgroups, but became moderately cost-incurring with respect to TUT for most subgroups.

We increased the rate at which patients with moderate and severe iron overload could cease taking chelation medication when on a regular programme of automated RBCX. This information from clinical advisers came too late in the preparation of the economic submission to be incorporated into the base case and the full sensitivity analysis. The results from this scenario indicate that chelation costs are substantially reduced in these patient groups. Automated RBCX with the Spectra Optia system becomes cost–saving in comparison to both manual RBCX and TUT in all patient subgroups, with one exception. In children treated for primary stroke prevention with severe overload automated RBCX is cost-neutral with respect to TUT. A 1-way sensitivity analysis on this latter subgroup indicates that automated RBCX becomes the lowest cost treatment option when chelation costs exceed £9,766 per year, a situation that is very likely in patients with severe iron overload.

There are few realistic circumstances in which manual RBCX is a lower cost option than automated RBCX over 5 years. Automated RBCX with the Spectra Optia system is highly likely to be at least cost-neutral in comparison to manual RBCX and TUT over 5 years in the majority of SCD patients, and in many cases should be massively cost-saving.

9.5.10 What are the key drivers of the cost results?

The key drivers that increase the procedure costs when using Spectra Optia system are:

- Consumables – Spectra Optia exchange set
- Increased use of RBC units – this can be minimised by using depletion/RBCX protocols where appropriate, which can reduce RBC use by up to 2 units per procedure

The key drivers of the cost savings when using the Spectra Optia system are:

- Avoidance or reduction of chelation therapy
- Reduction in hospital admissions for complications of SCD such as

painful crisis, ACS or secondary stroke

- Savings in staff time in comparison to manual RBCX

Miscellaneous results

9.5.11 Describe any additional results that have not been specifically requested in this template. If none, please state.

We have not included the capital and maintenance costs of the Spectra Optia system in the de novo economic model so far. This is because it is a multi-purpose device which can be used for more than just automated RBCX. There are around 59 hospitals in England and Wales that already own at least one Spectra Optia system and around 27 that have the capability to provide automated RBCX using it. At least one of the clinical advisers had access to a device but was unable to use it for this purpose and another wanted to expand their use of the device to include non-automated RBCX procedures. Other haematology services have at least 2 devices for use in elective exchange for SCD patients.

We can estimate the number of patients that can be accommodated by a single Spectra Optia system. This could range from 60 (3 patients per day, with an interval of 4 weeks) to 160 (4 patients per day, interval of 8 weeks). The largest treatment centres in the UK each have around 40-60 SCD patients on long term transfusion programmes. This means that most haematology departments that purchased a Spectra Optia system would have spare capacity, allowing the device to be used for plasma exchange, stem cell harvesting, etc.

In the worst case scenario, where the entire capital and maintenance cost of the device is included in our model the total additional cost over 5 years would be £52,052.45 plus 5 × £4,572, or £74,912.45. In the base case scenarios there is a maximum saving per patient of £52,517 between automated and manual RBCX (adults with mild iron overload) and £51,888 between automated RBCX and TUT (adults with no iron overload). Even in a relatively small SCD haematology centre with 5 regular patients, the device costs would equate to an extra cost of around £15,000 per patient. This is very likely to be

outweighed by the savings identified in Table C11.1 (section 9.5.2) in all but the most severely iron overloaded patients.

Five years is a short timescale over which to amortise the capital costs. Ten years is a more appropriate lifespan for such technology (the Cobe Spectra system has been in use for around 27 years). Also, by restricting our model to a 5-year time horizon we have substantially underestimated the cost savings that would continue to accrue after this period from reduced chelation therapy, strokes and hospital admissions. Therefore this economic model indicates that the realisable savings from the continued use of automated RBCX are likely o greatly outweigh the increased upfront technology costs of the Spectra Optia system.

9.6 Subgroup analysis

For many technologies, the capacity to benefit from treatment will differ for patients with differing characteristics. Sponsors are required to complete section 9.6 in accordance with the subgroups identified in the scope and for any additional subgroups considered relevant.

Types of subgroups that are not considered relevant are those based solely on the following factors.

- Subgroups based solely on differential treatment costs for individuals according to their social characteristics.
- Subgroups specified in relation to the costs of providing treatment in different geographical locations within the UK (for example, if the costs of facilities available for providing the technology vary according to location).

9.6.1 Specify whether analysis of subgroups was undertaken and how these subgroups were identified. Cross-reference the response to the decision problem in table A1 and sections 3.2 and 7.4.4.

The model has already considered subgroups related to age (weight) and iron overload status on the basis differential RBC volume requirements, procedure

time and chelation use. Additional subgroup analysis is not supported by sufficient published evidence.

9.6.2 Define the characteristics of patients in the subgroup(s).

See previous section.

9.6.3 Describe how the subgroups were included in the cost analysis.

See previous section.

9.6.4 What were the results of the subgroup analysis/analyses, if conducted? The results should be presented in a table similar to that in section 9.5.1 (base-case analysis).

See previous sections.

9.6.5 Were any subgroups not included in the submission? If so, which ones, and why were they not considered?

Other subgroups were not supported by sufficient evidence to warrant producing additional analyses.

9.7 Validation

9.7.1 Describe the methods used to validate and cross-validate (for example with external evidence sources) and quality-assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical and resources sections.

The collation of published values used to determine the model parameters was quality checked by another analyst. The cost analyses identified in the literature search was not deemed to be suitable as a source of validation material. The model assumptions and some of the parameters were provided to and commented on by several clinical advisers.

9.8 Interpretation of economic evidence

9.8.1 Are the results from this cost analysis consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

There were no rigorous published economic analyses identified in our literature search that could be used for validation of our model results. The cost reviews that we identified in section 8.1 were simplistic and poorly reported, so that it is difficult to identify exactly what resources and costs have been included. None of these followed changes in patient chelation use over time and none used a UK perspective.

As expected, we identified that per procedure costs were higher for automated RBCX with the Spectra Optia system than for the other types of regular transfusion.

9.8.2 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?

Yes

9.8.3 What are the main strengths and weaknesses of the analysis? How might these affect the interpretation of the results?

The strengths of the model are:

- The model compares automated RBCX against both transfusion modalities that are in common use in the UK
- Many of the parameters used are based on values collated from several published studies, many of which are relatively recent.
- 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 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 model takes into account several important clinical outcomes (stroke, hospital admissions, need for chelation therapy) that have not previously been identified as costs.

- 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 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.

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

The weaknesses of the model are:

- 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.

- 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.

- 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.

- 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.

- Capital and maintenance costs for the Spectra Optia system were not included in the model due to the variety of service implementations. The impact of these was analysed separately.

9.8.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

Data on the rates at which patients start and cease chelation therapy using different regular transfusion modalities would provide a more robust basis for the economic model. This data should already exist in patient clinical records and could be accomplished by local audit, providing data to determine cost estimates for local implementation plans.

The model is particularly sensitive to the number of procedures per year and the number of RBC units used per procedure. Again, this data could be relatively easily identified from local records.

Some of this data may be available already in the National Haemoglobinopathies Registry, but is not available in their published reports.

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10 Appendices

10.1 Appendix 1: Search strategy for clinical evidence (section 7.1.1)

The following information should be provided:

10.1.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

Medline, Medline inprocess and Embase were searched online using Ovid. Scopus, Pubmed, Econlit, Cochrane database and Web of Science were searched using their respective websites.

For the extended literature search only Medline, Medline inprocess, Embase and the Cochrane database were searched due to time constraints.

10.1.2 The date on which the search was conducted.

The initial literature search was conducted on 03 June 2015. The second, extended literature search was conducted on 09 and 10 June 2015.

10.1.3 The date span of the search.

The search of the databases was not constrained. Selection of returned records was limited to 1993-2015.

10.1.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

The first search strategy was conducted as follows:

Medline		
	Search term	**Results**
1	Anemia, Sickle Cell/	17280
2	sickle cell.tw.	17220
3	1 or 2	21043
4	Erythrocyte Transfusion/	6722
5	((red blood cell* or erythrocyte*) adj2 (exchang* or transfusion*)).tw.	3783
6	(red cell* adj2 (exchang* or transfusion*)).tw.	1510
7	erythrocytapheresis.tw.	144
8	apheresis.tw.	4899
9	or/4-8	14615
10	(terumo or optia or spectra or Cobe Spectra system or manual or automat*).tw.	284398
11	3 and 9 and 10	59

Medline in process		
	Search term	**Results**
1	sickle cell.tw	(1221)
2	((red blood cell* or erythrocyte*) adj2 (exchang* or transfusion*)).tw.	(345)
3	(red cell* adj2 (exchang* or transfusion*)).tw.	89
4	erythrocytapheresis.tw.	5
5	apheresis.tw.	309
6	(terumo or optia or spectra or Cobe Spectra system or manual or automat*).tw.	61276
7	2 or 3 or 4 or 5	737
8	1 and 6 and 7	4

Embase		
	Search term	**Results**
1	sickle cell.tw.	25952
2	sickle cell anemia/	27974
3	((red blood cell* or erythrocyte*) adj2 (exchang* or transfusion*)).tw.	6302
4	(red cell* adj2 (exchang* or transfusion*)).tw.	2652
5	erythrocytapheresis.tw.	227
6	apheresis.tw.	9874
7	erythrocyte transfusion/	16212
8	apheresis/	10089
9	apheresis device/	186
10	(terumo or optia or spectra or Cobe Spectra system or manual or automat*).tw.	417890
11	1 or 2	32535
12	or/3-8	32477
13	9 or 10	417958

14	14 11 and 12 and 13 (136)	

Scopus

(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*))

Cochrane Library (all relevant components)

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)

ECONLit

TX (terumo or optia or spectra or Cobe or automat* or manual) AND TX (erythrocytapheresis or apheresis or "exchange transfusion" or blood or erythrocyte* or "red cell") AND TX "sickle cell"

Web of Science

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

Pubmed (‘epub ahead of press’ search for ‘pubstatusaheadofprint AND key subject term’)

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

The additional extended search strategy was conducted as follows:

Medline		
	Search term	**Results**
1	Anemia, Sickle Cell/	(17326)
2	sickle cell.tw.	17276)
3	1 or 2	21104)
4	Erythrocyte Transfusion/	(6739)
5	((red blood cell* or erythrocyte*) adj2 (exchang* or transfusion*)).tw.	3793)
6	(red cell* adj2 (exchang* or transfusion*)).tw.	1514)
7	erythrocytapheresis.tw.	144)
8	apheresis.tw.	4909)
9	4 or 5 or 6 or 7 or 8	14647)
10	(terumo or optia or spectra or Cobe or manual or automat*).tw.	286206)
11	3 and 9 and 10	59
12	3 and 9	495
13	(exchang* or erythrocytapheres* or automat* or manual).tw.	374146)
14	12 and 13	158
15	14 not 11	99
16	transfus*.tw.	81766
17	3 and 9 and 16	380
18	14 and 16	104
19	18 not 11	66
20	15 and 19	66

Medline in process		
	Search term	**Results**
1	sickle cell.tw.	1227
2	((red blood cell* or erythrocyte*) adj2 (exchang* or transfusion*)).tw.	344
3	(red cell* adj2 (exchang* or transfusion*)).tw.	89
4	erythrocytapheresis.tw.	5
5	apheresis.tw.	308
6	(terumo or optia or spectra or Cobe or manual or automat*).tw.	61556
7	2 or 3 or 4 or 5	735

8	1 and 6 and 7	4
9	(exchang* or erythrocytapheres* or automat* or manual).tw.	49860
10	1 and 7 and 9	10
11	10 not 8	6

Embase		
	Search term	**Results**
1	sickle cell.tw.	25993
2	sickle cell anemia/	28007
3	((red blood cell* or erythrocyte*) adj2 (exchang* or transfusion*)).tw.	6316
4	(red cell* adj2 (exchang* or transfusion*)).tw.	2656
5	erythrocytapheresis.tw.	227
6	apheresis.tw.	9883
7	erythrocyte transfusion/	16262
8	apheresis/	10097
9	apheresis device/	187
10	(terumo or optia or spectra or Cobe or manual or automat*).tw.	418792
11	1 or 2	32581
12	or/3-8	32543
13	9 or 10	418861
14	11 and 12 and 13	136
15	(exchang* or erythrocytapheres* or automat* or manual).tw.	538895
16	9 or 15	539020
17	11 and 12 and 16	341
18	17 not 14	207

Cochrane Library (all relevant components)

#1	"sickle cell":ti,ab,kw and exchang* or erythrocytapheres* or automat* or manual:ti,ab,kw (Word variations have been searched)
#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 3"exchange transfusion" or blood or erythrocyte* or "red cell":ti,ab,kw (Word variations have been searched)
#3	#1 not #2

Pubmed (‘epub ahead of press’ search for ‘pubstatusaheadofprint AND key subject term’)

#1:	Search **pubstatusaheadofprint AND (exchang* or erythrocytapheres* or automat* or manual) AND "sickle cell"** Sort by: **Author**	8
#2:	Search (pubstatusaheadofprint AND (terumo OR optia OR spectra OR Cobe OR apheresis OR erythrocytapheresis OR manual OR automat*) AND "sickle cell") Sort by: Author	8
#3:	Search #1 NOT #2 Sort by: Author	1

ECONLit

S1	AB "sickle cell" AND AB (exchang* or erythrocytapheres* or automat* or manual)	0
S2	TI "sickle cell" AND TI (exchang* or erythrocytapheres* or automat* or manual)	0
S3	S1 OR S2	0

10.1.5 Details of any additional searches, such as searches of company or professional organisation databases (include a description of each database).

Terumo provided a database of complaint information.

10.1.6 The inclusion and exclusion criteria.

Inclusion criteria	
Population	Sickle cell disease, including all subtypes
Interventions	Spectra Optia or Cobe Spectra devices described as automated red cell exchange procedures, including depletion/exchange and IHD-RBCX for chronic programmes of treatment
Outcomes	Any outcome listed in the scope plus alloimmunisation
Study design	Not restricted in search criteria
Language restrictions	English
Search dates	1993 – present day
Exclusion criteria	
Population	Patients being treated for sickle cell crisis emergencies, mixed populations where data could not be disaggregated. (Note that Perseghin et al, 2015 has been included to demonstrate

	equivalence of the RBCX procedure in Cobe and Optia devices.)
Interventions	Automated cell exchange where the device could not be identified. One-off treatments, e.g. before surgery or during pregnancy.
Outcomes	Any additional outcomes with no immediate clinical reference
Study design	Case reports were excluded due to the large number of observational studies available
Language restrictions	Non-English language
Search dates	Pre-1993

10.1.7 The data abstraction strategy.

The full results of the literature database searches were exported into Reference Manager. Records were then sifted by title and abstract by two people independently. 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.

Data was extracted from the full text of studies into tables B6, B8 and B9. These were adapted as required, as the level of detail and information provided in each study varied significantly. Data extraction was checked by a second member of the Cedar team.

10.2 Appendix 2: Search strategy for adverse events (section 7.7.1)

The following information should be provided.

10.2.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

No separate search strategy was used to identify adverse events.

10.2.2 The date on which the search was conducted.

See above

10.2.3 The date span of the search.

See above

10.2.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

See above

10.2.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

See above

10.2.6 The inclusion and exclusion criteria.

See above

10.2.7 The data abstraction strategy.

See above

10.3 Appendix 3: Search strategy for economic evidence (section 8.1.1)

The following information should be provided.

10.3.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- EconLIT

- NHS EED.

Medline, Medline inprocess and Embase were searched online using Ovid.

Scopus, Pubmed, Econlit, Cochrane database and Web of Science were searched using their respective websites.

10.3.2 The date on which the search was conducted.

03 June 2015

10.3.3 The date span of the search.

As the protocol for conducting red blood cell exchange was first published in 1994 (Kim et al 1994) references prior to 1994 were deemed to be irrelevant.

10.3.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Medline search:

	Search term	**Results**
19	Anemia, Sickle Cell/	17280
20	sickle cell.tw.	17220
21	1 or 2	21043
22	Erythrocyte Transfusion/	6722
23	((red blood cell* or erythrocyte*) adj2 (exchang* or transfusion*)).tw.	3783
24	(red cell* adj2 (exchang* or transfusion*)).tw.	1510
25	erythrocytapheresis.tw.	144
26	apheresis.tw.	4899
27	or/4-8	14615
28	(terumo or optia or spectra or Cobe or manual or automat*).tw.	284398
29	3 and 9 and 10	59

10.3.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

None

10.4 Appendix 4: Resource identification, measurement and valuation (section 9.3.2)

The following information should be provided.

10.4.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- NHS EED
- EconLIT.

No additional literature search was conducted for resource use. The studies identified in the clinical evidence were used. Where data was sparse or missing studies that used unidentified or alternative devices were included and key studies in top-up transfusion.

10.4.2 The date on which the search was conducted.

NA

10.4.3 The date span of the search.

NA

10.4.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

NA

10.4.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

None

10.4.6 The inclusion and exclusion criteria.

NA

10.4.7 The data abstraction strategy.

NA

11 Related procedures for evidence submission

11.1 Cost models

An electronic executable version of the cost model should be submitted to NICE with the full submission.

NICE accepts executable cost models using standard software – that is, Excel, TreeAge Pro, R or WinBUGs. If you plan to submit a model in a non-standard package, NICE should be informed in advance. NICE, in association with the External Assessment Centre, will investigate whether the requested software is acceptable, and establish if you need to provide NICE and the External Assessment Centre with temporary licences for the non-standard software for the duration of the assessment. NICE reserves the right to reject cost models in non-standard software. A fully executable electronic copy of the model must be submitted to NICE with full access to the programming code. Care should be taken to ensure that the submitted versions of the model programme and the written content of the evidence submission match.

NICE may distribute the executable version of the cost model to a consultee if they request it. If a request is received, NICE will release the model as long as it does not contain information that was designated confidential by the model owner, or the confidential material can be redacted by the model owner without producing severe limitations on the functionality of the model. The consultee will be advised that the model is protected by intellectual property rights, and can be used only for the purposes of commenting on the model's reliability and informing comments on the medical technology consultation document.

Sponsors must ensure that all relevant material pertinent to the decision problem has been disclosed to NICE at the time of submission. NICE may request additional information not submitted in the original submission of evidence. Any other information will be accepted at NICE's discretion.

When making a full submission, sponsors should check that:

- an electronic copy of the submission has been given to NICE with all confidential information highlighted and underlined
- a copy of the instructions for use, regulatory documentation and quality systems certificate have been submitted
- an executable electronic copy of the cost model has been submitted
- the checklist of confidential information provided by NICE has been completed and submitted.

- A PDF version of all studies (or other appropriate format for unpublished data, for example, a structured abstract) included in the submission have been submitted

11.2 Disclosure of information

To ensure that the assessment process is as transparent as possible, NICE considers it highly desirable that evidence pivotal to the Medical Technologies Advisory Committee's decisions should be publicly available at the point of issuing the medical technology consultation document and medical technology guidance.

Under exceptional circumstances, unpublished evidence is accepted under agreement of confidentiality. Such evidence includes 'commercial in confidence' information and data that are awaiting publication ('academic in confidence').

When data are 'commercial in confidence' or 'academic in confidence', it is the sponsor's responsibility to highlight such data clearly, and to provide reasons why they are confidential and the timescale within which they will remain confidential. The checklist of confidential information should be completed: if it is not provided, NICE will assume that there is no confidential information in the submission. It is the responsibility of the manufacturer or sponsor to ensure that the confidential information checklist is kept up to date.

It is the responsibility of the sponsor to ensure that any confidential information in their evidence submission is clearly underlined and highlighted

correctly. NICE is assured that information marked ‘academic in confidence’ can be presented and discussed during the public part of the Medical Technologies Advisory Committee meeting. NICE is confident that such public presentation does not affect the subsequent publication of the information, which is the prerequisite allowing for the marking of information as ‘academic in confidence’.

Please therefore underline all confidential information, and highlight information that is submitted under ‘commercial in confidence’ in blue and information submitted under ‘academic in confidence’ in yellow.

NICE will ask sponsors to reconsider restrictions on the release of data if there appears to be no obvious reason for the restrictions, or if such restrictions would make it difficult or impossible for NICE to show the evidential basis for its guidance. Information that has been put into the public domain, anywhere in the world, cannot be marked as confidential.

Confidential information submitted will be made available for review by the External Assessment Centre and the Medical Technologies Advisory Committee. NICE will at all times seek to protect the confidentiality of the information submitted, but nothing will restrict the disclosure of information by NICE that is required by law (including in particular, but without limitation, the Freedom of Information Act 2000).

The Freedom of Information Act 2000, which came into force on 1 January 2005, enables any person to obtain information from public authorities such as NICE. The Act obliges NICE to respond to requests about the recorded information it holds, and it gives people a right of access to that information. This obligation extends to submissions made to NICE. Information that is designated as ‘commercial in confidence’ may be exempt under the Act. On receipt of a request for information, the NICE secretariat will make every effort to contact the designated company representative to confirm the status of any information previously deemed ‘commercial in confidence’ before making any decision on disclosure.

11.3 Equality

NICE is committed to promoting equality and eliminating unlawful discrimination, including paying particular attention to groups protected by equalities legislation. The scoping process is designed to identify groups who are relevant to the evaluation of the technology, and to reflect the diversity of the population. NICE consults on whether there are any issues relevant to equalities within the scope of the evaluation, or if there is information that could be included in the evidence presented to the Medical Technologies Advisory Committee to enable them to take account of equalities issues when developing guidance.

Evidence submitters are asked to consider whether the chosen decision problem could be impacted by NICE's responsibility in this respect, including when considering subgroups and access to recommendations that use a clinical or biological criterion.

For further information, please see the NICE website (www.nice.org.uk/aboutnice/howwework/NICEEqualityScheme.jsp).